Centre de recherche en cancérologie Nantes-Angers

Rapport Hcéres

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agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit

Centre de Recherche en Cancérologie Nantes-Angers

From the

Université de Nantes

Université d'Angers

INSERM

CNRS

January 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

January 2011

Research Unit

Name of the research unit: Centre de Recherche en Cancérologie Nantes-Angers

Requested label : UMR_S INSERM, UMR CNRS

N° in the case of renewal : UMR_S 892

Name of the director: Mr Jacques LE PENDU

Members of the review committee

Committee chairman

Mr Charles THEILLET, Université de Montpellier 2, Montpellier

Mr Renato MONTEIRO, Université Paris 7, Paris

Other committee members

Ms Urzsula HIBNER, Université de Montpellier, Montpellier

Mr Angelo VACCA, University of Bari, Italy

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Report

1 • Introduction

- Date and execution of the visit

The visit took place on January 18 and 19, 2011. Two separate subcommittees examined on the one hand the Immunology Department, and on the other hand the Cancer and Radiobiology Departments. The visit began at 9 am on January 18 began by a general presentation of the Research Center by the Director. Then the subcommitteees met individually with each team. On the second day, they met the students/post-docs, technicians and scientists during split meetings. Each subcommittee then convened for drafting the reports. After a final gathering of the two subcommittees, the vist ended at 5 pm on January 19.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

CRCNA is a recent structure created as an Inserm Research Center (INSERM U892) in 2008. The Director for the finishing 4 year term is Mr Marc Bonneville, who will pass the responsibility over to Mr Jacques Le Pendu for the next term. As future Director, Mr Le Pendu made all presentations concerning the Center.

CRCNA comprises 250 people, including 32 research staff appointed by Inserm or CNRS, 52 University staff (associate and full-prof), 48 PhD students, 15 post-docs, 72 technical staff.

One of its peculiarities is that its research facilities are located on 3 different sites respectively in Nantes (main laboratory gathering 13 teams), St Herblain (CRLC facility, 2 teams) and Angers (CRLC, 2 teams).

CRCNA is structured in 3 departments:

Department 1: “Immunology and Immunotherapy”; coordinated by Mr Marc Bonneville, 8 teams.

Department 2: “Oncogenesis and targeted therapies” coordinated by Mr François Vallette, 7 teams.

Department 3: “Immunospecific targeting of radiopharmaceuticals” Mr J. Barbet/Ms F. Kraemer-Bodéré , 2 teams.

Scientifically, oncology and immunology are the common links between all teams and research projects.

Two committees were missioned for the evaluation of this Center and Department 1 was evaluated by the Immunology committee directed by Renato Monteiro, whereas Departments 2 and 3 were evaluated by the Cancer committee headed by Charles Theillet

- Management team

The management team is professionnally and straightforwardly organized. The Director is assisted on an every day basis by a deputy director. They work with a Directory board to which also participate the coordinators of each department. A strategic committee involves leaders of each team, and the CRCNA council comprises representative form each team, core facility, post-docs and students. In addition, the Center is guided by an external Scientific Advisory Board.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	47	51
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	31	33
N3: Number of other researchers including postdoctoral fellows (Form 2.2 2.4 and 2.7 of the application file)	23	44
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	37 ETP 31.75	39 ETP 31.85
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	46 ETP 36.75	
N6: Number of Ph.D. students (Form 2.8 of the application file)	48	
N7: Number of staff members with a HDR or a similar grade	68	67

2 • Overall appreciation on the research unit

- Summary

This Research Center has been set up 5 years ago and officially created as an INSERM Research center in January 2008 including 13 teams from Nantes and two merging teams from Angers. Most of the teams from Nantes moved to a new building (IRT) last year. It has a strong potential to become a center of excellence in cancer research in France notably a reference center for the West region.

Overall personnel benefit from a good work environment, at least in the newly integrated building in Nantes.

Staff scientists have set up active connections with local partners, being proactive participants in technological platforms and IFR management, have strong and long lived collaborations with clinical partners and a well structured network of international academic and industrial collaborations.

Technical and administrative personnel have expressed positive appreciations about working conditions and integration in the Center. About 50% of them work on technological facilities and all enjoy a good level of autonomy. They are actively involved in training young researchers. A general problem is the large proportion of technicians and engineers that are on temporary positions, with a number of them nearing the 6-year contract limit. Solutions are been actively sought by the direction, but the discontinuation of some contacts may be highly detrimental to the center given the know-how these personnel centralize.

Students and post-doctoral fellows also benefit from a good environment in terms of material, space and financing. Although the number of students may seem appreciable, team leaders have repeatedly pointed to the drop in new appointments of students in the doctoral school. The number of post-docs is fair but not outstanding for a structure of this size.

Research outputs: The unit has a significant research output in terms of publications. The large number of national and international collaborations participates in this output. The different teams published close to 500 original articles in the past 4 years (without redundancy), among which >60 with an impact factor >10. Despite of a very good scientific output testified by this large number of publications, the center still lacks publications of very high visibility in prestigious journals. As other outputs, we can list two spin off companies, 11 patents emanating from the 3 departments, two of which being licensed, and several industrial partnerships.

The Center has organized a number of common technical facilities as well as open technological platforms. It is of note that the proposed director has been very active in the past four years in structuring open platforms as a director of the IFR 26 in Nantes University.

Synergistic added value of the Center is high. The center is organized around easy access common facilities and shared technical rooms. It has fostered highly active interactions and numerous collaborations among teams belonging to the same department. It seems that cross department collaboration could be improved. This goal has been considered as a priority by the Center management for the coming four-five years. Stronger interactions would benefit to a number of groups working in the oncology department and developing immunology related projects.

Teaching and training: The unit is actively involved in the training of masters and PhD students, as well as in the teaching of immunology and oncology. It is the most important immunology group in Nantes/Angers, and has an important responsibility in teaching these disciplines. It is integrated in the life sciences department of the universities of Nantes and Angers. As compared to other units/departments, it is large and very productive with a good visibility. The universities support its activities in immunology, oncology and radiobiology. 52 PhD theses have been defended.

Future developments: The center plans to continue developing research in oncology and immunology related to cancer. An important perspective is the validation of research findings in human disease settings. The center currently has several clinical connections based on each individual project, and these should be strengthened. Clinical collaborations should also facilitate the identification of biomarkers. A project of SIRIC (Comprehensive Cancer Center) has been set up and submitted as part of the recent INCa call. This proposal ambitions to gather forces in academic research and clinics working on cancer in Nantes and Angers within one large structure. This move will assemble research teams, teaching personnel and clinical staff distributed in 2 Universities and 4 hospitals within a single administrative structure.

Last, recruitment of young researchers should also be an important perspective, in particular in teams without full-time scientists.

- Strenghts and opportunities

- International, national, and local visibility;
- Active partnerships and collaborations with national and international groups;
- Strong capacity in raising external funds;
- High number of well-structured common technical facilities and open technological platforms;
- New building in Nantes with very good lab settings;
- Strong interaction with several clinical departments;
- Clear niche in translational research;

- Strong partnership with the clinical cancer center (IRCNA) and well defined interactions as part of the SIRIC project;
- Strong support by both Universities in Nantes and Angers;
- High number of patents and start-ups;
- Good connections with industrial partners.

• Weaknesses and threats

- Creation of new teams is essentially based on burgeoning of former teams. In some cases it has appeared to the committee as a way to resolve conflicting situations between seniors.
- No incoming young group from outside and no plans to hire promising junior-scientists (Avenir/Atipe, ERC, or ANR-jeune chercheur).
- CRCNA teams are dispersed over 5 buildings in 3 cities. This was considered as potentially worrisome for the groups in Angers. This will clearly be a challenge for the management team, which will have to find ways to keep scientific communication and contacts ongoing despite the distance.

• Recommendations

- Improve international visibility of the center beyond the strong reputation of some individuals;
- Bring together all teams to a single building at least those working in Nantes;
- It has been noted that the Center has not yet set up a central seminar program. External seminars are up to individual groups. This can only be recommended;
- As part of internal scientific communication, the Center could have the young scientists (PhD and post-docs) organize on a yearly basis workshops where students and post-docs present their work. This is done in other research center and is quite successful;
- Set up an international call aiming at hiring young researchers and giving them the opportunity to create their own group. However, this will only be possible if the Center has open lab space available. The committee did not get a clear picture on this point nor did it have the impression of a clear intention to call for application of young promising researchers working abroad and applying to AVENIR/ATIP grants.

• Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	49
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	30
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.94
A4: Number of HDR granted during the past 4 years	5
A5: Number of PhD granted during the past 4 years	52

3 • Specific comments

- Appreciation on the results

The unit has a significant research output in terms of publications. The large number of national and international collaborations participates in this output. The different teams published close to 500 original articles in the past 4 years (without redundancy), among which >60 with an impact factor >10. Despite of a very good scientific output testified by this large number of publications, the center still lacks publications of very high visibility in prestigious journals.

As other outputs, we can list two spin off companies, 11 patents emanating from the 3 departments, two of which being licensed, and several industrial partnerships.

52 PhD theses have been defended.

17 phase I/II clinical trials have been completed.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

Most team leaders and occasionally staff members have been invited to international meetings.

The attractiveness is till limited since for instance no incoming young group from outside has been recruited and there are no clear plans to hire promising junior-scientists (Avenir/ATIP, ERC, or ANR-jeune chercheur).

The fund raising activity is quite good. It amounted to 4.6 M€ in 2008 and 2.7 in 2009 including 1.2 and 0.4 M€ from international grants, respectively.

Several teams are participating and/or coordinating national or international networks.

The valorization output is particularly good with several patents, two spin off companies and many industrial contracts.

- Appreciation on the management and life of the research unit

The management appeared very good. A deputy director assists the Director on an every day basis. They work with a Directory board to which also participate the coordinators of each department. A strategic committee involves leaders of each team, and the CRCNA council comprises representative form each team, core facility, post-docs and students. In addition, the Center is guided by an external Scientific Advisory Board.

There are frequent team and department meetings, PhD students presentations, and an annual retreat of the whole center.

Synergistic added value of the CRCNA is high. The center is organized around easy access common facilities and shared technical rooms. It has fostered highly active interactions and numerous collaborations among teams belonging to the same department.

The unit is actively involved in the training of masters and PhD students, as well as in the teaching of immunology and oncology. It is the most important immunology group in Nantes/Angers, and has an important responsibility in teaching these disciplines.

- Appreciation on the scientific strategy and the project

The Center management has considered the improvement of cross department collaboration as a major goal for the coming four-five years. Stronger interactions would benefit to a number of groups working in the oncology department and developing immunology related projects.

An important perspective is the validation of research findings in human disease settings. The center currently has several clinical connections based on each individual project, and these should be strengthened.

At this time, the teams do not contribute to the budget of the center. It is envisioned that a fee will be taken on grants to support core facilities and shared actions. This is to be encouraged in order to allow risk-taking projects.

4 • Appreciation team by team

Team 1: Immunobiology of non-conventional T lymphocytes

Project leader: Mr Marc BONNEVILLE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties	2	4
N2: Number of full time researchers from research organizations	2	3
N3: Number of other researchers including postdoctoral fellows	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position	3	6
N5: Number of engineers, technicians and administrative staff without a tenured position	0	0
N6: Number of Ph.D. students	2	2
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

The new team 1 is a merger of the previous teams 1, 2 and 8. Altogether, the newly formed team 1 has an international reputation in the field of human γδ and αβ T-cell biology including clinical aspects, and strong expertise in ADCC. This team is internationally leading in the field of identification of γδ T-cell ligands. They were the first to characterize phosphorylated ligands for human γδ T-cells. More recently, one of the team members was involved in the identification of ecto-F1 ATPase as a novel tumor ligand for γδ T-cells. Recent work has addressed the interaction of γδ T-cells with DCs, the potential role of butyrophilin-related molecules for γδ T-cell activation, and the modulation of γδ T-cell activation by NK receptors. Moreover, the group has optimized the conditions for induction of γδ T-cell reactivity towards tumor cells (i.e., identified an important role of IL-21). In addition, the group also characterizes novel ligands for unconventional human αβ T-cells, with a focus on mycobacterial

glycolipids. The newly developed methods to synthesize such ligands will help to explore the potential of such unconventional αβ T-cells in immunotherapy. Former team 2, now part of team 1 has performed in-depth characterization of the T-cell receptor selection of virus-specific αβ T-cells. Former team 8, now part of team 1, has a particular interest in ADCC and the usage of adoptive transfer of EBV-specific T-cells for therapy of post-transplant lymphoproliferative disease. The observation of CD16 expression on ab T cells in lymphocytosis and the engineering of CD16-expressing T cells for cell immuntoherapy is original and of interesting therapeutic potential.

The publication list of the 3 PI's comprises 39 peer-reviewed papers since 2006, mostly in (very) good (e.g. Blood, Hepatology, J. Immunol.) journals, which is an impressive output. In addition, several invited reviews in top-ranking journals (Nat Immunol, Nat Rev Immunol, Immunity) reflect the international visibility of the group. Outstanding original publication in Immunity in 2005.

There are long-term interactions with prominent groups in France and outside France (e.g., Italy, Germany, US).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This group is well established at the international level and has a longstanding and excellent reputation in the field of unconventional and T-cells.

The team recruited post-docs and PhD students regularly. There are no post-docs/PhD students recruited from abroad.

Funding abilities of the team are very good: 1.2 Mio € since 2006 through EU projects and national grants including involvement in 2 EU grants (previous team 1), 310 K€ from ANRS/ANR (previous team 2), 640 K€ from international and national sources (previous team 8). Total sum of > 2 Mio € since 2006 is a very good success rate.

National and international collaborations are well established.

Results of research have been published in international peer-reviewed journals. 1 patent on iNKT ligands, priviliged connection with Innate Pharma (Team 1 leader is co-founder), and commercialization of several anti-TCR mAb illustrate significant socio-economic output.

- Appreciation on the scientific strategy and the project

In view of their suspected role at the crossroad of innate and adaptive immune responses, the in-depth characterization of ligands recognized by γδ T-cells, their activation requirements, interaction with other immune cells, and exploitation of their immunotherapeutic potential is of high relevance. The proposed work on the role of CD277 for the TCR-dependent activation of human γδ T-cells is highly original and of tremendous interest, also with regard to the potential anti-tumor reactivity of γδ T-cells. Similarly, the proposed experiments to explore the immunotherapeutic potential of γδ T-cells (role of IL-21, anti-CD277 mAb) are important and relevant to the field. Subproject #2 addresses conventional MHC-restricted αβ T-cells. Investigators plan to characterize in detail unique subsets of MHC class I-restricted human CD4, and to follow-up specific T-cell responses in transplant patients and HCV-infected patients using highly sophisticated multiparameter flow cytometry for detection of very rare antigen-specific T-cells. Again, this is not only (clinically) highly relevant but also highly original. Subproject # 3 characterizes ADCC sensitivity of human myeloma cells and develops innovative tools for analysis of ADCC with murine mAb. Experiments proposed by investigators to generate a range of CTL transduced with different murine/human FcR constructs (murine FcγRIIIα / human FcεRIγ) are innovative and important for improvement of ADCC in hematological malignancies. This group also proposes to explore adoptive transfer of autologous EBV-reactive CTL in SLE patients, an interesting proposal in view of the discussed role of EBV for SLE. Subproject #4 includes transversal programs aimed at analysis of the role of prostglandins for regulation of αβ and γδ T-cell responses to glioblastoma and the large-scale generation of new anti-TCRγδ mAb for potential therapeutic application.

- Conclusion

– Summary

The committee considered this team of excellent level that made essential contributions in their field. The work performed by team 1 is cutting edge at an international level in T-cell biology. It is the most experienced team in France and one of the most famous in the world in this field. Projects combine highly original basic research with the exploitation of clinical relevance. The publication level of this team is very good notably in review articles.

– Strengths and opportunities

- International visibility, cutting edge research in T-cell biology;

- Original and outstanding projects;

- Very good level of publications (PNAS 2007, Immunity 2005), several good papers in specialized journals (Blood, J Immunol, Hepatology, etc) and outstanding review papers in Nat Rev Immunol 2010, Immunity 2008, Immunol Rev 2007, Nat Immunol 2006, etc);

- Strong in raising external funds;

- Merging the 3 previous teams makes sense because of shared methodologies and complementary expertise in human T-cell biology.

– Weaknesses and threats

No obvious weakness.

– Recommendations

Overall, the proposed scientific strategies represent an impressive combination of basic and applied research.

Improve the quality of original publication level as previously done.

Team 2: Clinical and translational research in skin cancer

Project leader: Ms Brigitte DRENO

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	10
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	0
N7: Number of staff members with a HDR or a similar grade	1

- Appreciation on the results

The team leader is a clinician who has been previously working together with team 2 investigators on the development of cellular based (TIL) immunotherapeutic approaches to treat cutaneous cancers. The team leader's important contributions were to provide evidence for the beneficial effect of adoptive therapy of TIL on relapse prevention in melanoma patients (J Invest Dermatol 2009, Canc Immunol Immunother 2007). She also contributed to the identification of some relevant Ag recognized by such TIL such as Melan-A, MELOE-1 and -2 (J Exp Med 2008, Cancer Immunol Immunother 2010). More recently she has become interested in studying the prognostic value of the presence of Tregs in tumor infiltrating LNs from metastatic melanoma patients (Exp Dermatol 2008) as well as the study of the expression of tumor specific genes (Arch Dermatol Res 2009).

During the last 5 years the team leader published 7 last author papers in Cancer Immunol Immunother, J Invest Dermatol, Eur J Dermatol, Exp Dermatol, Arch Dermatol…

In addition, her contribution has been absolutely essential for a large part of the output of team 3 (e.g. J Exp Med 2008).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This is a new team clearly dedicated to clinical and translational research activity, with essentially clinicians and engineer/technicians belonging to the Hospital (no PhD students and post-doc), many of them with only part time dedicated to research activity.

Being a new team, it is therefore too early to evaluate the management of the team.

The team leader has already supervised 5 PhD students.

- Appreciation on the scientific strategy and the project

The project is oriented towards clinical and translational research in skin cancer, and strong collaboration/interactions will be maintained with team #3. The first axis of research is dedicated to the development of clinical trials to validate previous works (TIL vs abstention phase III trial) or to evaluate combined gene therapy (TIL + intratumoral injection of Ad-IFNg vector) in melanomas patients; or Imiquimod (TLR7 ligand) in Lentigo maligna patients. The second axis is a follow up of previous works aimed at evaluating the impact of the tumor microenvironment on disease progression. They will seek for molecular/cellulars markers able to predict patient prognosis. This will be assessed in tumor invaded LN from metastatic melanoma patients by measuring gene mutation events in melanoma cell, expression of tumor Ag, analysis of immunosuppressive cytokine/chemokine production, and the presence of Foxp3+ Tregs through the analysis of the methylation status of Foxp3 promoter region in order to focus on "true" Tregs. The last axis will deal with epidemiology and the development of educational programs for primary and secondary prevention of skin cancers.

- Conclusion

  - Summary

Team 2 is a new team issued from team 3 that has made important contributions in the past together with scientist from team 3. The committee considered this team important for the CRCNA for the future development of translational research on melanoma. Projects are clinically oriented and appear feasible considering their expertise in clinical research. There are, however, structural problem due to the absence of full-time scientists in the team.

  - Strengths and opportunities

The team leader has a strong international reputation in the clinical development of immunotherapeutic approaches in melanoma. They developped a GMP grade facility and all technologies for TIL-based cell therapy of melanoma. The prior results of clinical trials are very impressive. Beside a local and national network of active collaborations the team leader participated to several clinical trials with academics and industrial partners, with one major ongoing project with a phamarceutical company.

  - Weaknesses and threats

Although the team leader has published 7 senior author papers since 2007, in good journals appropriate to the field, the number of publications in journals with high impact factor appears quite limited. While understanding and appreciating the underlying rationale, the committee considers the establishment of two different groups in the scientific area of melanoma research a potential risk.

  - Recommendations

Because, the translational research program of this team is of a major importance for CRCNA, the committee supports this team and encourages the team leader to recruit a full-time scientist.

This proposal comes with the specific recommendation that this team strongly needs to work in very close collaboration with team 3.

Team 3 : Anti-tumor T cell responses and immunotherapy

Project leader: Ms Nathalie LABARIERRE

- Staff members

N1: Number of researchers with teaching duties	5
N2: Number of full time researchers from research organizations	1
N3: Number of other researchers including postdoctoral fellows	1
N4: Number of engineers, technicians and administrative staff with a tenured position	4
N5: Number of engineers, technicians and administrative staff without a tenured position	0
N6: Number of Ph.D. students	5
N7: Number of staff members with a HDR or a similar grade	4

- Appreciation on the results

Team 3 has a very well-defined focus on the analysis of both spontaneous and therapy-induced tumor-specific T cell responses. The way in which clinical material is used to further research and in which basic research findings are used to design new clinical protocols are highly admirable, and an example of how translational work should be set up. In particular the work on adoptive T cell therapy and on strategies to develop defined tumor-specific T cell products are timely and internationally competitive. Productivity of the team has certainly been good. However, in view of the high value of the work, an even higher prominence/ output could perhaps have been expected.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Impact of the work of this team has been significant, but - as mentioned above- perhaps slightly below what one would expect when looking at the quality of the work. In line with this, visibility as reflected by invited seminars is not extensive. The funding of the situation is not completely clear, in particular with respect to the (expensive) clinical translation of the peptide vaccines and cell therapy products that the team is currently developing.

- Appreciation on the scientific strategy and the project

The long-term goals of the group are well-defined and in large part aim to address important questions. The competitive position of the group is very good, both because of the established link between research and clinic, and because a large part of the research effort focuses on topics that have been developed by the team itself (e.g. the Meloe antigen, the technology for antigen-specific T cell purification). Competitive position in smaller parts of the research program is somewhat less strong. In particular the research effort on non-conventional T cells is considered too diffuse and would benefit from a stronger focus. Based on the available data, the strong focus of the team on the characterization of the Meloe antigen is justified. However, a risk does exist that the role that

this antigen plays in melanoma recognition is less than is currently expected, something of which the group is aware.

- Conclusion

  - Summary

The committee considered that this is a very solid group that made several original and important discoveries in the field of melanoma. The team has a quite good level of publications with original papers (i.e. J Exp Med 2008) and good funding level despite of a relatively poor international visibility. They are developing novel technologies with direct relevance for human therapy.

  - Strengths and opportunities

- Very strong competitive position at the interface between research and clinic, ability to translate research findings in new clinical protocols;

- Topics generally well-chosen;

- Excellent level of publications

- Capacity to develop novel technologies with direct relevance for human therapy.

  - Weaknesses and threats

No obvious weakness.

International visibility may be further improved.

  - Recommendations

Strong link with the team 2 must be maintained to ensure continued high profile productivity in the translational field.

Team 4 : Biology of dendritic cells and immunotherapeutic use in oncology

Project leader: Mr Marc GREGOIRE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties		1
N2: Number of full time researchers from research organizations		4
N3: Number of other researchers including postdoctoral fellows		1
N4: Number of engineers, technicians and administrative staff with a tenured position		1
N5: Number of engineers, technicians and administrative staff without a tenured position		0
N6: Number of Ph.D. students		2
N7: Number of staff members with a HDR or a similar grade		1

- Appreciation on the results

Team 4 (T4) has a long-standing expertise in the biology of dendritic cells (DC) and currently i) investigates ways of conditioning DC for therapeutic use and ii) explores strategies inducing tumor cell apoptosis that could also initiate an adaptive anti-tumoral immune response. T4 has made several important contributions regarding optimal ways to generate and mature monocyte-derived DC, including in AML patients. The research line on "immunogenic apoptosis" has lead to the important observation that attenuated measles virus induces oncolysis of mesothelioma cells and favors DC-mediated cross-priming of CD8+ T cells. The team has also invested a lot of efforts to identify combinations of epigenetic drugs (hypomethylating drugs and histone deacetylase inhibitors) that induce death of malignant pleural mesothelial (MPM) cell lines and increase their immunogenic status, by exploiting their panel of human MPM cell lines and developing mouse models. These results are however so far not published. All the research line dealing with mesothelial cancer, also not yet fully valorized in terms of publication, is of valuable importance as this disease remains so far incurable and not much studied.

The group has published a large number of papers in specialty journals (since 2006, 45 publications including Cancer Research, Cancer Sci., Exp. Hematol., Scand. J. Immunol. and 2 Immunotherapy as last author), including two publications with good IF (Cancer Research, Am J Pathol). The team's work has also lead to 1 European patent application for treating mesothelioma. The productivity is ranked as good, but the team should be encouraged to increase publications in high impact journals. The team has also supervised 4 PhD theses since 2006, which is a rather good output given the rather limited size of the team

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader has a good visibility, as attested by several invitations to meetings (mostly national) and active participation to the DC-THERA European network of Excellence. 3 "Chargés de recherche" (2 CR1 Inserm and 1 CR1 CNRS) with complementary expertise, 2 joined the team in 2008 and 2009, which is obviously a healthy sign. Such reinforcement in staff scientists together with an expected increase in the level of publications should

increase the international visibility of the team. They have gathered and access to a large collection of MPM cell lines.

Team's fund-raising capacities are good.

The team has developed stable partnership notably through appropriate national collaborations for development of oncolytic MV vaccine and HDAC inhibitors and tight interactions with the CIC Biotherapy of Nantes Hospital. In addition, the team is part of an FP6 Excellence Network. No international collaborations are mentioned.

Socio-economic output. 1 European patent. The output in terms of potential benefice for the patients is at this stage difficult to evaluate, but the team has already contributed to the identification of diagnosis markers for mesothelial cancer.

- Appreciation on the scientific strategy and the project

The projects largely build up on the expertise and recent results of the team and capitalize on already established collaborations. The projects on immunogenic cancer cell death in the mesothelia model are somehow risky in the sense that immunological cell death has became an increasingly competitive area and the committee was not convinced about team leadship in this area. The particular focus on the clinical transfer of their results seems justified and ambitious.

- Conclusion

  - Summary

Team 4 is a well-structured group of full time scientists with a long-standing expertise in the biology of dendritic cells exploring strategies for cell therapy as well as inducing tumor cell apoptosis to mount an adaptive anti-tumoral immune response. Projects are promising but need focusing to go deep in the mechanism to improve results quality. The team has a medium level of publications despite of a relatively good funding.

  - Strengths and opportunities

Recruitment of two young permanent full time scientists.

Strong biobank on mesothelioma.

Strong interface with pneumologists in the Thorax institute.

  - Weaknesses and threats

Few papers published in high IF journals

Too many non complementary projects

  - Recommendations

Improve the quality of publications by more focused research in mechanistic processus

Team 5 : Glycoconjugates in immune responses

Project leaders: Mr Jaques LE PENDU and Mr Frédéric ALTARE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties	1	1
N2: Number of full time researchers from research organizations	2	2
N3: Number of other researchers including postdoctoral fellows	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position	0	0
N6: Number of Ph.D. students	5	1
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

The general topic of this team is to analyse the role of selected glycoconjugates in host-pathogen interaction. The team results from the recent association of two team leaders with proven expertise on glycoconjugate biology and who supervise two groups within the team. Team 5's interest in glycoconjuates concerns 3 areas of research:

(i) Team 5 demonstrated that Histo-Blood Group Ags are receptors for caliciviruses which are responsible for most of gastroentiritis outbreaks worlwide and a major health problem in under-developed countries. They studied the evolution of glycosyltransferase genes, giving rise to the view that they play a decisive role in host-pathogen interaction. This led to the proposal of a model where glycosyltransferase gene co-evoluate with caliciviruses as a mechanism of protection at the population level (herd innate protection).

(ii) Because of the well established competence of one of the team leader on glycoconjugates and based on connections with other teams interested with T lymphocyte immunology within the CRCNA, the team recently developped a project on the identification of endogenous glycolipid ligands for iNKT cells. They interestingly characterised beta-glycosylceramides (beta analogs of the well described alphaGal-Cer) as such new iNKT cell ligands.

(iii) A topic on mycobacterial glycoconjuates was introduced through the recent arrival of one of the team leader. He developped an original and reliable in vitro system to model of human mycobacterial granuloma formation which reproduces cell differentiation and organisation seen in patient's granuloma. Based on this model, he made important contributions to the role of M.tb. glycolipids for granuloma formation, to the characteriation of virulent M.tb.-induced Multi-Giant Cells, and to identification of foamy macrophages as a shelter for dormant non-replicative M.tb. Promising preliminary results on the interactions of MGC and foamy macrophages with unconventional T cells (iNKT and gamma-delta T cells) have been produced as well. This model is also used to identify novel anti-tubercular drugs able to target dormant mycobacteria.

Taken as a whole, progress of Team 5's work looks quite impressive, the research is relevant and original even though the diversity of the project is high. Of note are the remarkable evolution of the calicivirus project from the molecular evidence of calicivirus interaction with HBGAg toward the demonstration at a population level (in wild rabbit cohorts) of the herd innate protection concept, and the recognized validity of the in vitro granuloma model as attested for instance by numerous requests for collaboration from academic teams/pharma industries and a review published in the high-ranking journal Nature Immunology.

The team published 31 papers in peer-reviewed international journals among which 13 are signed as senior author by one or the other team leader (IF mostly between 4 and 6.5 IF and 2 in the high-ranking Plos Pathogens, IF9). Probably because issues studied by the team do not fall into the current hot topics of Immunology, they publish in journals of modest ranking, however this does not detract the overall quality and originality of the results.

Team members filed 1 patent on methods to produce analogs of alpha-gal-cer.

Shared interest and expertise of both team leaders for infectious diseases and glycoconjugates is manifest. Yet, the partnership is recent and they did not publish together thus far. The promising common project which relies on the identification of potential endogenous iNKT ligands in granuloma foamy macrophages did not start yet.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Both PI are regularly invited in international conferences.

The team recruited 2 post-docs from Göteborg university and one PhD student from Porto and 3 PhD student defended their thesis during the last period.

The team displays an excellent ability to raise funds as shown by successful application to 6 ANR contracts, 2 European networks (FP6, FP7), industrial contracts and charities.

The participation to international or national scientific networks, existence of stable collaborations with foreign partners. They mention stable partnerships with foreign partners from Porto, Goteborg, and London.

Team members filed one patent on iNKT ligands and due to the reliability of the in vitro granuloma model they participate to clinical trials on the evaluation of new drugs against tuberculosis. Two members of the team are founding members of a biotech company (CEERAM) and they obtained industrial contracts with 3 companies (GSK, Archivel Pharma and IBD company).

- Appreciation on the scientific strategy and the project

The project plan is a logical extension of the previous work. The established in vitro granuloma model will be used to further characterize the interplay between M.tb. and foamy macrophages, and to characterize the fate of intracellular bacteria in more detail. The planned analysis of the role of T-cells raises opportunities for collaboration with other Teams of CRCNA (e.g. #1). The planned screening for potentially novel anti-tuberculosis drugs based on the established in vitro granuloma model seems useful and has already received funding. The outlined continuation of the Herd Innate Protection concept is promising, as is the identification of endogenous ligands for human iNKT cells. It is further planned to add a new topic, which is to explore the potential use of C-type lectin receptors for cancer immunotherapy. Team #5 is experienced to explore the proposed strategy of arming CTL with chimeric C-type lectin/Signal transduction receptors although no results have been generated yet on this part.

Athough well-connected to each other, specific projects on caliciviruses and on the immunomodulation by M tuberculosis are pursued by each group on their own. It was obvious however that both groups benefit from each

other and are keen to develop novel synergistic projects, particularly on the identification of endogenous iNKT ligands produced in foamy macrophages. Together, the proposed continuation of the projects seems reasonable and feasibility of the 4 year projects is supported by prior published results, original preliminary observations and shared skills of the groups. Impact of the results could be important (new knowledge on host-pathogen interaction in general and identification of new ligands of iNKT and antitubercular drugs specifically).

All ressources are shared between both groups.

Albeit in a highly competitive field, the endogenous iNKT ligand project holds an interesting potential because it relies on the complementary skills of both groups and is supported by original results on beta analogs of alpha-GalCer.

- Conclusion

  - Summary

The committee considered this team well structured with 2 PI focusing on infectious diseases and glycoconjugates. A new imput was provided by the recruitment of new PI working on immunomodulation by M tuberculosis. Projects are interesting addressing mechanistic pathways and searching for new potential therapy. The team has good level of publications and good funding.

  - Strengths and opportunities

This partnership between two experts of glycoconjugates is promising and is supported by solid preliminary results. The collaborative work on iNKT ligands is a potential powerful resource.

  - Weaknesses and threats

Several different projects are proposed and this would probably benefit from greater focus.

  - Recommendations

The committee thus strongly recommends to reinforce links between the existing 2 sub-groups by building common themes. In this regard, the team should consider to strengthen the analysis of iNKT ligands in foamy macrophages.

Team 6 : Cytokines and receptors in immuno-hemato-oncology

Project leaders: Mr Yannick JACQUES et Ms Sylvie HERMOUET

- Staff members

N1: Number of researchers with teaching duties	2
N2: Number of full time researchers from research organizations	3
N3: Number of other researchers including postdoctoral fellows	1
N4: Number of engineers, technicians and administrative staff with a tenured position	3
N5: Number of engineers, technicians and administrative staff without a tenured position	3
N6: Number of Ph.D. students	3
N7: Number of staff members with a HDR or a similar grade	2

- Appreciation on the results

The research of this team developed along 2 main axes : the biology of IL-15 and its receptor studied, and cytokine deregulation in hematological malignancies.

Along the first axis of research, this group made some important contributions leading to a better understanding of the structure and mode of action of the IL-15 receptor. This allowed them to design a fusion molecule with IL-15 and its soluble receptor, that turned out to act as an IL-15 superagonist. This is an original research that provides important tools to address basic science questions regarding the physiological role of IL-15, but that also has important potential applications.

The second line of research has focused on the JAK2 V617F mutation in patients with myeloproliferative neoplasm. This group contributed to a better characterization of the occurrence of this mutation in such myeloproliferative disorders.

The quality of the research is illustrated by 33 articles over the last 5 years in (very) good journals such as J.Biol.Chem. Blood, Nature Immunol., Gastroenterology and J.Exp.Med, and by the fact that the number of citations of the 2 principal investigators has been increasing along the last 5 years.

Important partnerships have been established including collaborations with J. Di Santo or E. Vivier that led to high level collaborative publications based on the tools developed by this group.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

One of the team leaders is an internationally recognized expert in the field of IL-15. Beside the quality of the basic research mentioned above, Gastroenterology and J.Exp.Med., this work has a major biotechnological aspect which is reflected by 5 patent applications, one licensing agreement and the creation of a spin-off company.

Both principal investigators are very active in their field and participate to international meetings and networks such as an European network on the molecular diagnosis of MPN that they coordinate (COST action). One of the team leaders is responsible for the organization of the annual cytokine meeting of the SFI.

The team has been successful in raising funds and to develop collaborations with industrial partner. For instance one of the team leaders is currently coordinating a major project for the development of small molecule inhibitors of IL-15.

- Appreciation on the scientific strategy and the project

Both group established fruitful collaborations with experts in the field.

Recently, the recruitment of an additionnal after a successful postdoctoral stay in the US (first author of an Immunity and of a J.Exp.Med. paper) represented a great opportunity for the team to extend its expertise to pathophysiological models where the role of IL-15 and its receptor can be further studied.

- Appreciation on the project

The part of the project dealing with IL-15 structure and antagonist development is clearly defined, feasible and vey strong. The contribution of the newly recruited researcher will allow adding a physiological side to this project, by taking advantage of the models he developed during his postdoctoral stay. This evolution of the group is a significant strategic development, and is expected to be fruitful.

The project proposed by team 6 appears very ambitious and some aspects dealing with the structure of JAK2 mutants and their mode of interaction with cytokine receptors might be far fetched, considering the fierce competition in this field. Other aspects such as the HGF/IL-11 pathway probably represent a more promising avenue of research that would be more original and likely to better fit the competences demonstrated by this group in the past.

- Conclusion

  - Summary

This team has a national and international reputation in the field of cytokines and cancer, notably on IL-15 biology. Projects are well-structured and well-designed addressing mechanistic pathways and new therapeutic approaches. The team has good level of publications, excellent collaborative projects and excellent industrial collaboration. Team leader is a co-founder of a start-up.

  - Strengths and opportunities

- International reputation of the senior investigators.

- Strong biotechnological orientation and expertise of the IL-15 project.

- Recent recruitment of a young investigator who is expected to extend the expertise of the team to in vivo animal models using gene-targeted mice.

  - Weaknesses and threats

- Some parts of the project dealing with JAK2 mutations might be overambitious based on the actual expertise of the group and the competition in the field.

- Beside this specific issue, there is no obvious weakness.

– Recommendations

Maintain high level of publication by focusing the efforts of the group on the original lines of research where they are really competitive.

Team 15: Innate Immunity, Immunopathology and Immunotherapy

Project leader: Mr Yves DELNESTE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties	8	9
N2: Number of full time researchers from research organizations	1	1
N3: Number of other researchers including postdoctoral fellows	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position	6	6
N5: Number of engineers, technicians and administrative staff without a tenured position		
N6: Number of Ph.D. students	5	5
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results

This is a well-established group with an international recognition in the field of innate immunity receptors. During the past five years the group has focused its research activities on the biology of innate immune cells, the development of antitumoral immunotherapy strategies based on targeting vaccine antigens to some Pattern recognition Receptors (PRR), the mechanisms involved in the generation of immunosuppressive myeloid cells. More recently they have been interested in the study of PRR (PTX3) as potential target of autoantibodies in autoimmune diseases.

The major findings are:

The demonstration that a subset of neutrophils can express CCR7 and migrate to the lymph nodes were they can cross-present Ag to CD8 T Cells (Blood 2011 & 2007);

The demonstration that neutrophils can express the long pentraxin PTX3 which are soluble PRR involved in the recognition and elimination of certain pathogens. In close collaboration with a team in Milan, they sowed that PTX3 stored in neutrophils has a central role in neutrophil-mediated resistance against infection by A. fumigatus

(J Exp Med. 2007); and that the PTX3 molecule can re-localized to the membrane of apoptotic neutrophils, and is perceived as a late-eat me signals by phagocytes (Cell Death Differ. 2009);

Concerning the study of the mechanisms responsible of the generation of immunosuppressive myeloid cells in ovarian cancer, they showed that IL-6 and LIF produced within the tumor are involved in the generation of these cells that is overcome by T cell-derived IFN-γ (Blood 2007, Int J Cancer 2009).

The identification of the molecule NS3 from hepatitis C virus through its capacity to bind to DC via SRs SREC-I and SR-A1 (J Hepatol, 2010). They are currently evaluating its ability to induce cross-presentation of antigens that are associated and to induce protective antitumor responses.

Close connections has been established with the departments of clinical Hematology and Immunology at Hospital of Angers leading to a quite impressive list of publications.

The committee felt that the group has successfully addressed important question on the influence of innate receptors on innate and adaptive immunity and made important contributions in the field.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The achievement of the previous projects was very good to excellent, with an international standard of scientific production, as attested by a high number of publications in middle to high peer-reviewed Journals (J Exp Med, 3 Blood, J Hepatol, Cell Death Diff). The group has established long-lasting and productive international and national collaborations with academic partners as well as private companies.

- Appreciation on the scientific strategy and the project

This is a quite large group including mainly Clinicians/Researchers with teaching duties, 4 technicians/ingeniors, 5 PhD student and 3 post-docs. The group may need some implementation in the future by recruiting young scientists since only the team leader has a full time research position. The two PhD students who have been recently trained in the group have an impressive list of publications as first authors in top journals (J Exp Med, Blood , Cell Death Diff , EJI) which is a sign of the high quality of the scientific management inside the team. The team has successfully applied for competitive grants (ANR) and have been able to raise considerable funds over the past 5 years.

Most of the projects presented by the team are in direct continuation of the results they have obtained over the past few years. Four research axes are going to be developed around the master denominators of innate immunity and of antitumor immunotherapy.

These 4 Axes include:

i) Biology of innate immune cells; with studies on a) the role of Il-6 and LIF in monocytes/DCs generation and b) characterization of neutrophils as APCs;

ii) The role of Soluble pattern recognition receptors (PPR) in apoptosis and autoimmunity, with a particular focus on Clusterin and Anti-PTX3 autoantibodies.

These two aspects have been most productive the past 5 years and should be the main projects of the laboratory. Of note it is worthwhile to remember the current highly competitive field in innate immunity.

iii) The thrid axis is on Cancer Immunotherapy with development of vaccine strategy (mostly on basic immunological mechanisms), control of immunosuppressive myeloid cells (taking advantage of Axis 1 results on LIF and IL-6). These 2 points make real sense giving the first 2 research axes.

iv) Axis 4 focuses on oncogenesis of AML taking a crucial main advantage of the transcriptome facility at Angers University. The project has just been started and the visiting committee was impressed by the preliminary results already obtained.

Although the number of projects seems quite high, they are well structured and well supported by preliminary data.

- Conclusion

The committee concluded that this is an excellent group if one considers the scientific production.

– Summary

The committee considered this team excellent, a well-structured team established at Angers with several full-time scientists who made original discoveries in innate immunity and cancer. They made important contributions in the past and have promising prospects for the future development of translational research i.e. the development of antitumoral immunotherapy strategies based on targeting vaccine antigens to some Pattern recognition Receptors, the mechanisms involved in the generation of immunosuppressive myeloid cells. Team 15 has an excellent level of publications based on original articles.

– Strengths and opportunities

The committe was impressed by the straightforward presentation of the past activity and the clear formulation of the future research projects that were well supported by encouraging preliminary results. Although the number of projects presented may appear quite numerous, the team has amply demonstrated its efficacy in the past. Also, the energy of this team in establishing high standard international collaboration, as well as strong collaborations with the local hematology and Immunology departments in Hospital of Angers was acknowledged.

Excellent level of publications (J Exp Med, Blood, …)

– Weaknesses and threats

No weaknesses were highlighted by the committee.

– Recommendations

Maintain the high level of publication by focusing the efforts of the group on the original lines of research linked to the CRCNA themes.

Team 17: Graft-vs.-Host reactions after allogeneic stem cell transplantation

Project leader: Mr Mohamad MOHTY

- Staff members

	Past	Future
N1: Number of researchers with teaching duties		1
N2: Number of full time researchers from research organizations		0
N3: Number of other researchers including postdoctoral fellows		1
N4: Number of engineers, technicians and administrative staff with a tenured position		3
N5: Number of engineers, technicians and administrative staff without a tenured position		3
N6: Number of Ph.D. students		2
N7: Number of staff members with a HDR or a similar grade		1

- Appreciation on the results

The team leader is a clinician (PU-PH) with a known expertise in the field of allogeneic stem cell transplantation who recently joined the CRCNA in 2008. This is a newly created group. The team leader has been leading a research project in previous team #4 during the past two years with 1 PhD student and 1 technician on histone deacetylase inhibitors on DC phenotype and function in vitro. Although some results have been obtained they still appear quite preliminary.

The number of publications of the team leader is impressive with more than 60 papers in the last 5 years. Most publications arise from clinical activity, many of them signed as first authors (11) in very good journals Blood (4), Leukemia (2) since 2007 and 5 as senior authors in journals with lower impact factors (Br J Hematol, Bone Marrow Transplant, Biol Blood Marrow Transplant, Haematologica..).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Strong international visibility based on clinical work as attested by the high number of invitations in international meeting and his participation to the editorial board of international journals (Leukemia, Haematologica).

The team leader has raised numerous and very important fundings since 2006 from various national sources (Association pour le Recherche contre le Cancer, Fondation de France, PHRC, DHOS) and private companies (Pierre Fabre, Amgen, Roche, Genzyme) which is a reflect of national recognition.

This team is well integrated within the CRCNA as well as within the local scientific and clinical community.

- Appreciation on the scientific strategy and the project

This a new team with 3 technicians and 3 PhD students. The size of the team is therefore relatively small and it is too early to evaluate the management of the team.

It is also too early to evaluate the capacity of the Team leader to supervised PhD students (3 ongoing PhD, past-PhD supervision not mentioned).

The team leader has planned to recruit a full-time scientist to firmly establish the group within the next coming years.

- Appreciation on the project

Based on its published results and expertise, this newly established team proposes a research program aimed at studying the role of CD4+ Th cell subsets and dendritic cells (DC) particularly plasmacytoïde DC (pDC) in the pathophysiology of GVHD in human. The main objectives are i) to characterize the Th subsets and pDCs infiltrating the target tissues during GVHD, ii) to identify predictive factors for GVHD incidence and severity through the longitudinal monitoring of various cytokines, including IL-12 family members and others biomarkers in the blood of allo-SCT patients, iii) to study the impact of cellular composition (DC content) of the allogeneic stem cell graft on GVHD, and finally iv) the impact of immunomodulatory agents (proteasomes inhibitors, HDAC inhibitors) on DC/pDC functions, which is a follow-up of the recent activity of the team leader in previous Team #4.

Although, the proposed projects might identify new potential therapeutic targets (and possibly new area of research?), they are perhaps too many given the size of the group. Fundamental questions such as the impact of donor-derived DC composition or HDAC inhibitors on GVHD were not clearly addressed. This part of the project may strongly benefit of suitable experimental models to really assess the relevance of pDCs or other DC subsets as potential regulators of T cell alloreactivity in GVHD.

- Conclusion

  - Summary

This team is headed by a young group leader, which has a strong potential due to a very good fundamental-clinical interface and design of challenging projects. Good publication record, mainly issued from the clinical activity, which is of international standard.

  - Strengths and opportunities

The committee was impressed by the highly dynamic and enthusiastic way the team leader presented his past and present activities, as well as by the capacity of the team leader to raise important funding during the past few years.

  - Weaknesses and threats

The team may need some implementation in the future by recruiting a full-time scientist in order to develop the ongoing projects in an effective way.

The projects appear too many given the size of the group and concentration on fewer projects will allow more in depth analysis.

  - Recommendations

The committee suggests to the team leader to try to validate the experimental hypothesis on the role of pDC/ Th17 subsets in acute GVHD in animal models allowing mechanistic studies in order to validate the experimental results which will be mainly obtained from human biopsies.

Team 7: Cell survival and tumor escape in breast cancer

Team leader : Mr Philippe JUIN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	/	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	/	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	/	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	/	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	/	
N6: Number of Ph.D. students (Form 2.7 of the application file)	/	
N7: Number of staff members with a HDR or a similar grade	/	4

- Appreciation on the results

Regulation of cell death and survival by Bcl2-related proteins is of pivotal relevance for tissue homeostasis. The pathogenesis of many widespread diseases, including cancer, can be traced back, at least partly, to abnormal expression/activity of Bcl2 family members. Accordingly, the field attracts attention of a huge number of groups and is thus highly competitive. While the knowledge on the molecular, cellular and biological functions of Bcl2-related proteins is in many aspects quite detailed and deep, translation of this knowledge into clinical and diagnostic practice lags behind. In this regard, a clear strength of team 7 is its expertise and focus on preclinical and translational aspects of Bcl2-related research. Based on their previous key finding that Bax is activated by a conformational switch induced by binding of BH3 domain-only proteins (Cartron P et al.. Mol Cell. 200), team 7 demonstrated that inhibitors of prosurvival Bcl2 family members alone can already be sufficient to trigger apoptosis in some tumor cells. Their work on Bcl2 inhibitors places the group in a niche of clinical importance where they not only have the chance to gain international visibility but also have in view clinical practice.

The publication record of team 7 is respectable in terms of number and quality of the publications. In particular, Juin and colleagues signed 10 studies (including a just recently published study in Mol Cell Biol not listed in the written report) as first or senior authors in high-ranking Journals with impact factors reaching from 4 to 11. The core publications of team 7 (7.31, 7.10, 7.5 and Gautier et al. Mol Cell Biol. 2010 Dec 20) are of high quality and have a clear impact as they deliver a ratio how pharmacological manipulation of the Bcl2-Bax interplay can be exploited for therapeutic purposes.

Team 7 has been originated from former team 9 early after creation of the CRCNA and accordingly there are many experimental and conceptual connections with team 9. For example there are several publications co-authored by teams 7 and 9. The separation of the former team 9 in two independent teams is satisfying in view of the different tumor entities that are covered by the two teams but it is recommended to continue the very successful partnership between both teams.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The international reputation/visibility of the team is good and mainly based on a couple of high ranking papers (JCB, Genes & Development, Mol. Cell) of the team leader in the last decade. As most of these publications originated from cooperative work with team 9, it is, however, currently difficult to distinguish between the recognition of both groups. The team has successfully applied for funding from various sources. This includes competitive funding from Fondation de France (coordinator P Juin) and INCa (not as coordinator), as well as ARC, Ligue etc. There are also several industrial contracts. Particularly the latter emphasizes the strength of team 7 in the "niche" of Bcl2-related translational research

The team leader has been invited twice as speaker in international meetings..

- Appreciation on the scientific strategy and the project

The proposed project has two major aims. Firstly, identification of markers of Bcl2-dependence of breast cancer tumors including their relation to the established breast cancer classification. This topic includes assessment of tumor cell response to Bcl2 inhibitors and thus has a clear clinical perspective. Secondly, the investigation of the interplay between Bcl2-dependence and various general aspects of tumor cell biology such as EMT, DNA damage repair, etc. The first goal is straightforward and the consequent continuation of the previous work of team 7. The only point not clearly envisioned in this context is the use/perspective of appropriate animal models. The second aim is broad and diversifies in several comprehensive subprojects. It is feasible to do some initial experiments on all aspects listed in the application but it will be presumably very important to focus on the most promising subproject(s) as early as possible.

- Conclusion

  - Summary

Team 7 is a relatively new group headed by a young group leader. The project is a straightforward preclinical continuation of previous basic science work on the mechanisms of Bax activation and apoptosis induction. It is methodically up to date and well integrated in the research activities of the CRCNA.

  - Strengths and opportunities

Translational nature of the project

High potential for cooperation with other teams of the department

  - Weaknesses and threats

In the written report and particularly in the oral presentation P. Juin presented an impressive number of good ideas how the major topics of the project can be developed in the future. In view of the limited resources, however, there is a need for concentrating attention on some of them.

  - Recommendations

Incorporation of animal models for testing the therapeutic potential of Bcl2 inhibitors in "Bcl2-dependent" tumor models

With respect to the relationship of Bcl2-dependence and general aspects tumor cell biology – focusing on one or two clearly defined aspects

Team 9: Apoptosis and Tumor Progression

Team leader : Mr François VALLETTE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	8	5

- Appreciation on the results

This team has a long-standing record of significant contributions to the understanding of fundamental mechanisms of cell death, in particular by performing detailed analysis of interactions of members of the Bcl2 family. The focus of their current research is on cancer and more precisely on aggressive brain tumours: glioblastoma (GBM) and grade IV astrocytoma. In the last four years the team described a variant of Bax lacking a N-terminal portion of the full-length protein that occurs in a significant % of GBM. This observation led to a description of mitochondrial localization signal of Bax and, in a close collaboration with the team 7, to exciting data regarding interactions of Bax with BH3-only Bcl2 family proteins. The study of Bax activation and its targeting to mitochondria opened two further areas of investigation: Bax/lipid interactions and interactions of different Bcl2 proteins with components of the mitochondrial translocase complex. Another theme that has been actively pursued by the group is the impact of perturbations of glucose metabolism (pharmacological inhibition of pyruvate dehydrogenase kinase) on autophagy and apoptosis. Interestingly, this led to the study of tumoral versus normal neural stem cells (rat model, extended to human samples). While this is a major, vast field of investigation, the results pertaining to Bcl2, which switches from anti-apoptotic to pro-apoptic action in DCA-treated cancer stem cells, links this study to the core of the team's research interests. Finally, the team has engaged in a study of epigenetic control of apoptosis-related gene expression in glioblastoma. While interesting, this approach remains rather descriptive for the time being. Overall, the team has engaged in a rich, original and varied research program in the last 4 years.

The team has made significant contributions both at the level of fundamental questions of regulation of programmed cell death and in describing specific mechanisms relevant to brain tumorigenesis. The publication record is very good: 23 articles emanating from the team and 12 more as collaborators, mostly in good, if not excellent, journals (Cell Death Differentiation, Oncogene, Cancer Res, one article in J Cell Biol). It is however noteworthy that several papers published in journals of moderate impact factors have in fact been highly cited (e.g. Apoptosis in 2007: 71x, JBC in 2004: 67x, two more JBCs in 2003 65x and 52x), indicating a true interest of

the community for the work of this team. Importantly, all major axes of research of the team gave rise to publications.

F Vallette has been invited several times to international meetings.

6 theses had been defended in the last 4 years.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The interesting evolution of the PI, whose expertise in basic aspects of apoptosis is internationally recognized, to more medically oriented research culminated in his taking up the direction of a translational facility, with a clear ambition of bringing new opportunities to patient care. He coordinates one of the axes of the Canceropole GO ("stem cells") and has a significant participation in teaching at the university.

The scientific production of the team has been presented at numerous meetings and seminars, both in France and abroad.

The team has been successful in obtaining grants (ANR Blanc, INCa, ARC, Ligue, as well as a joint French-South African program) and attracting young staff scientists. In the future further effort needs to be put into recruiting PhD students and post-docs.

They have organized several meetings on apoptosis.

- Appreciation on the scientific strategy and the project

The team proposes an ambitious project, largely based on continuation of the axes developed in the last 4 years. Mitochondrial import of Bcl2 family members will be studied with state of the art technology (BRET; proximity ligation in situ assay, proteomics). This is a traditional area of expertise of the team, which should be pursued.

Work on glucose metabolism and apoptosis regulation in glioblastoma is of major interest. The effort put into establishing a well controlled in vivo animal model should be encouraged, since it should allow to build a comprehensive experimental set up going from cell culture to patient derived samples.

Several recent publications from the group provide evidence of importance of epigenetic control of apoptosis related genes in glioblastoma. Moreover, this project is carried out in a close collaboration with clinical teams and has a clear translational potential. Care must be taken not to fall into a purely descriptive approach to this vast and complex subject.

Finally, the impact of prostaglandin signalling on tumour growth will be studied. The working hypothesis is the differential effects of PGE2 and PGD2 on the nontransformed cells in the tumour microenvironment. While clearly very interesting, this is yet another complex area of investigation, which might prove rather challenging to tackle.

- Conclusion :

  - Summary

The team develops high level original research. Their projects stem from their internationally recognized area of expertise, which is the mechanistics of mitochondrial control of apoptosis. For several years now they have taken a more medically oriented direction, focusing on Bcl2 family proteins in brain tumours. Modern state of the art technologies are used. The publication record is good and the team has developed solid collaborations, both locally and abroad.

– Strengths and opportunities

- Solid background in molecular mechanisms of apoptosis

- Good international recognition of the team's scientific production

- Strong collaborations with academic and clinical research groups

- Wide range of interests with the role of Bcl2 family proteins in carcinogenesis as an underlying focus (the wide intersts can also be a weakness…)

- The group appears attractive to young researchers

– Weaknesses and threats

- Care must be taken not to dilute too much the focus of the group

- While the size of the team has not diminished, it may be too small to tackle all the projects

- There are few students/post docs at the present time, although this has not been the case in the past, so it may just reflect an unfortunate coincidence of timing of the evaluation

– Recommendations

Care must be taken to recruit new students and post-docs and not to rely too strongly on researchers with heavy teaching duties

It may be wise to clearly define priorities in the different axes presented in the project. While they all appear interesting, they all require a considerable investment of resources and it is not entirely clear that the team will manage to efficiently carry out all the projects.

While the scientific reasons for independance of teams 9 and 7 are clear, both groups are likely to profit from the continued maintenance of a close collaboration between them.

Team 10 : Molecular bases for targeted therapies in Multiple Myeloma and Mantle Cell Lymphoma

Team leader: Ms Martine AMIOT

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number engineers, technicians and administrative staff with-out a tenured position (Form 2.6 of the application file)	3	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	4	4

- Appreciation on the results

The research activity of team 10 encompasses several issues on Multiple Myeloma (MM) and non-Hodgkin's lymphomas (NHLs), especially – among these – mantle cell lymphoma. On this basis, it collaborates with team 7 and 9. It is also closely linked to team 11.

The listed papers treat a modern aspect of MM, e.g., tailored therapies that should be matched with expression of specific plasma cell targets in well-defined patients or patients' groups. Special attention is given to patients with relapsed/ resistant disease, hence patients difficult to treat with conventional therapies.

Team 10 exhibits 51 papers in the 2006-2010 years of which 28 relate to the presented research program: 22 are focused on MM, mainly on signalling pathways, phenotypes and oncogenes of MM plasma cells; 14 are related to NHLs, particularly mantle cell lymphoma, and describe clinical aspects, including prognosis, diagnosis, and therapy; the remaining papers study breast cancer at the basic (1 paper) and therapeutic (2 papers) level. As a whole the scientific production is judged good to excellent. Papers are all published in appreciable-high IF journals (Br. J. Haematol., Haematologica, Cancer Res., Leukemia, Blood, J Immunology (n = 4)). They denote consolidate relationships between the team and other French groups involved in the myeloma research, hence a close French network, which includes the Intergroup Francophone du Myélome.

The work of PI, Mr. Amiot, is clinically oriented. It focuses on some biological events linked to drug resistance, therapeutic response, and death in patients with MM. It also validates the targeted therapies with respect to poor prognosis patients. In sum, her research issues are:

- Expression of Mcl-1 (an anti-apoptotic molecule) and resistance to bortezomib.

- Expression of Noxa (a pro-apoptotic molecule) induced by bortezomib.

- Association of the cleaved form of Mcl-1 and death following the melphalan and bortezomib therapy.

She exibits 12 papers related to research activity in 2006-2010: in eight she is last name, in four coauthor. The best scientific production is linked to 2006-2008 (papers published on Blood, J. Immunol., Oncogene), while in 2009-2010 only two significant papers are found. All the scientific activity is focused to the aims of the proposed research. Finally, papers imply a close collaboration with other French groups studying MM, and only in one paper the PI is linked to an USA group.

The PI is also involved in other research-related activities, including the organization of the Myelomax Society (a biotechnological Society pointing to the preclinical therapeutic studies on MM that emerged from this team), the collaboration with Industries producing drugs active on MM.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Although 5 Phd theses have been defended during the last 4 years, there are at this time no PhD fellows in the team.

The team seems quite stable as personnel, and no expansion is predicted in the future.

Senior members of the team have been invited to international meetings in France, Switzerland, Portugal, but not to the World Meetings on Multiple Myeloma and Related Malignancies, nor to similar meetings on Lymphomas.

The team does not seem to be inserted in an extra-French circle of studies on MM and NHL. This may be a weak point as to attraction of foreign scientists or students.

Funding is satisfactory and includes notably INCa grants.

- Appreciation on the scientific strategy and the project

The proposed project (2012-2015) focuses on MM and mantle-cell lymphoma to:

- Collect and characterize human material to obtain cell lines and define their molecular abnormalities (expression of Jag-2, p53, c-kit, Bcl-2, Mlc-1, chromosomal translocations).

- Identify new molecular targets for tailored therapy.

- Identify new markers of resistance.

- Design new clinical trials in conjunction with French groups.

The project is an expansion of the past one and should add new information on MM and lymphoma biology, and plausibly on new alternative therapies and new prognostic markers. However, the modern view on these diseases for therapy and prognosis is to consider both tumor cells and microenvironment cells (macrophages, endothelial cells, osteoclasts, mast cells, lymphocytes). At least 1-2 tasks of the project should be addressed to these cells. In addition, no translational tasks are proposed.

- Conclusion

  - Summary

The Amiot's team is working in depth on MM and mantle cell lymphoma biology, especially on mechanistic aspects of disease progresion, relapse, and resistance to therapy. The final goal is to find new markers among signaling proteins, oncogenes, and cell phenotype molecules that may be applied as prognostic and therapeutic markers. This can lead to identify new drugs and drug combinations that may be useful for tailored therapies and overcoming drug resistance.

– Strengths and opportunities

The main strength is that the Amiot's team is working on MM microenvironment, which is considered a new target for 'dual' therapy of the disease, i.e. to use drugs that target both plasma cells and microenvironmental cells that support the plasma cell growth and survival. This modern aspect of the MM therapy may lead to isolate new targets for tailored therapy (a modern approach to the MM therapy).

Also, the team is very united and linked to distinguished French groups working on MM. It is well-integrated in the CRCNA and sufficiently linked to the Minvielle's team that Is more focused on the clinical aspects of MM and clinical trials.

The team is using innovative techniques for the study of MM and mantle cell lymphoma.

– Weaknesses and threats

The group should finalize in vitro results on MM in preclinical models of MM. These are not mentioned in the future project. NHL are studied mainly on a clinical point of view. Basic/ translational research is lacking.

– Recommendations

Develop (or collaborate with other groups) for MM mouse models to study drugs against resistance markers.

Develop (or collaborate for) studies on basic/ mechanistic research on mantle cell lymphoma.

Clarify thematic positioning and interactions with team 11 which has very similar interests (MM, B cell malignancies and translational to clinical development). It would be counter productive if both teams did not cooperate.

Team 11: Integrative oncogenomics of multiple myeloma pathogenesis and progression

Team leader : Mr Stéphane MINVIELLE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	3
N5: Number engineers, technicians and administrative staff with-out a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	4	3

- Appreciation on the results

The work of this team is very translationally oriented. It is centered on molecular characterization of Multiple Myeloma (MM) and pursues three principal aims :

- Identification of molecular schemes underlying the progression from premalignant plasma cell disorder to malignant disease

- Identification of genetic changes predicting malignant progression

- Identification of molecular anomalies correlated to negative outcome and search for signatures predicting response to treatment.

As such the team is highly active in MM study groups in particular with the Intergroupe Francophone du Myélome (IFM) and participates in numerous clinical trials. This has given them access to a large number of clinical samples and allowed a number of interesting observations. Specifically the team of Stéphane Minvielle has defined expression signatures associated to disease progression and identified genes correlated to bortezomib resistance. It has also determined Copy Number Alterations and related expression changes correlated to prognosis. The final aim is the definition of a clinical decision scheme.

Scientific production expresses a good level activity, with a total of 61 articles listed of which a substantial part correspond to collaboration in large clinical trials where Team members contributed as co-authors. This testifies of the strong connection this team has with clinical groups acting in the MM field. Original papers where the team is leader (about 15) have been published in good to excellent level specialty journals (Leukemia (n = 3), Blood, J Clin Oncol (n = 4)).

The team leader has been invited to 3 international meetings.

Two patents have been filed.

The team is at the center of an excellent clinical network as testified by the high level recruitment of patients in clinical trials (about 70% of bone marrow biopsies from MM patients in France are sent to this team). The group is at the origin of Intergroupe Francophone du Myélome (IFM) of which a team member is the chairman.

In addition to the french speaking sphere, this team has also gained recognition from cognate groups in the US and participates to two international projects supported by NIH grants. In one of these the team acts as the reference lab for genetic profiling. It has also set up active collaborations with the Sanger Center in Cambridge, UK.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Senior staff members are well known and recognized in the MM field as testified by their activity as experts in national and international granting bodies and international collaborations.

No PdD theses have been defended and none is ongoing, which may be consecutive to the translational nature of the research.

The recruitment of post-docs should be improved but it seems that the team has plans and the funding to do so in a near future (as part of its collaboration with US groups).

The ability to raise funds is excellent as testified by the number of grants (INCa, PHRC) to which it is either partner or coordinator.

- Appreciation on the scientific strategy and the project

The project submitted is a continuation of the past work and includes novel questions, such as exome sequencing (ongoing with the Sanger) and splicing (whole exon-Affymetrix chips). Plans are to keep on characterizing MM at the molecular level and add refinements to existing decision charts.

The team is in leading position, both at the national, but also European level in its field and has set up collaborations to fulfill its aims.

- Conclusion :

  - Summary

The Minvielle's team is focused on the oncogenomic changes that take place in step with transition from MGUS to MM. These changes will be correlated to the progression phase (relapse, resistance to therapy, leukemic status) and the overall survival. The genomic changes will be studied at the functional level to understand the mechanisms of transition from MGUS to MM and of MM progression, as well as to identify new target for tailored therapy. These studies are parts of clinical trials (IM/DFCI 2009 – IFM / Celgene 07-01) carried out by the team in close collaboration with France and USA – MM Centres. The team is very well integrated in the CRCNA institution and represents a relevant research group.

  - Strengths and opportunities

A leading position in translational research on MM, at the center of the french MM network, strong links with international groups in the US.

Direct links with the clinic guaranteeing the translation of results in the clinical practice.

– Weaknesses and threats

Low number of young researchers, no PhD students and only one post-doc can turn into a limitation in the next few years, when time will come to replace outgoing seniors.

The group is focused on MM. As such it was able to become a reference in this field, but this may be too great a specialization.

– Recommendations

The group is mainly staffed by seniors and is largely composed of personnel with clinical duties. Efforts should be engaged to attract good post-doctoral level researchers and hire young permanent staff researchers. It may be beneficial to open the scope to other hematological malignancies.

Team 12 : Targeted therapies in colorectal cancer

Team leader : Mr Olivier COQUERET

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	4
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

One major aspect of the project developed by this team is to decipher the molecular mechanisms underlying resistance to several chemotherapy treatments in colorectal cancer. Their work is focused on the STAT3 transcription factor which is involved in several ways in this effect. In the past four years several interesting results have been obtained on the phosphorylation status of STAT3 in colorectal cancer, as well as on its target genes, PLK1 in particular of which activation can drive progression towards mitosis. They have also established that under DNA damage conditions Cdk5 activation leads via STAT3 to activation of the Eme1 endonuclease which will improve processing of damaged DNA. This team has also adressed the question of the inhibition of topoisomerase I on cell cycle arrest through the effect of Myc family members on regulation of the Aurora kinase. In this line it has also been shown that p21 and STAT3 participate in the inhibition of Myc and cdc25 in response to topoisomerase inhibition, thereby restoring senescence, but this effect is counteracted by the src-STAT3 pathway.

These results have been reported in several publications in good quality journals (J. Biol. Chem x 2., Cancer Res., Cell death & Differ). This part of the work has brought interesting contributions to the understanding of the role of STAT3 in response and resistance to treatments.

Another aspect of the work has concerned systematic proteomic studies of colorectal cancers. Methodological developments have been accomplished and more specific studies have led to identification of a neurotoxicity biomarker for oxaliplatin treatment. This approach has also allowed characterisation of a potential marker allowing identification of Kras mutated tumors. These developments are of potential interest in clinical monitoring of colorectal cancer patients. This proteomic work has been reported in two publications in speciality journals (J. Biomed. Biotechnol., Proteome Sci.)

Finally in a more translational approach the team has been implicated in several studies and clinical trials to improve therapeutic dosage on a rational basis. This has concerned analysis of the genetic variablity of metabolism enzyme of 5-FU and irinotecan, neurotoxicity of oxaliplatin and dose optimization of cetuximab. This

work of high clinical value has been reported in 13 publications in good (Clin Cancer Res., Br. J. Cancer) to very good level (J. Clin. Oncol.). A patent has been filed on this matter.

Overall it appears that a serious and productive work has been accomplished during the past four years, with a good equilibrium between fundamental studies, methodological developments and clinical analyses.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has been recently reinforced by the addition of a new assistant professor who will develop the STAT3-NF-kB2 part of the project. Renewal and growth of the team might be improved by hiring post-docs. The team also does not appear to be involved importantly in international collaborations which might be an important asset. Concerning the socio-economic interest of the activity there is a clear will to transfer the knowledge and to make it useful to patients treatment. It is noteworthy that the team contributed to the creation of two start-ups, Therapredict and ODPM. The latter one received the first prize of the French Research Ministry.

The various research projects have been financially supported by grants from Ligue, ARC and INCA.

- Appreciation on the scientific strategy and the project

The project will be in the continuity of the previous work and will be centered on the role of STAT3 and STAT3-NF-kB2 in resistance to treatments. Several questions will be addressed on the role of STAT3 and STAT3-NF-kB2 in cell cycle progression, DNA damage, autophagy and senescence regulation. All these studies will be conducted in the context of colorectal cancer cells.

The proteomic studies will also be pursued to obtain a proteomic map of tumor escape and to analyze the secreted proteins in response to chemotherapy.

Finally clinical research will be also pursued to optimize irinotecan dose and to evaluate the interest of associating it with sorafenib in patients with Kras-mutated metastatic colorectal cancer.

For the fundamental part the scientific developments are in logic continuation of the precedent studies with the interesting addition of the NF-kB2 subject.

- Conclusion :

  - Summary

The work conducted by this team is well-defined and addresses interesting subjects. The group is well-integrated in the CRCNA and its appartenance to the structure is an asset for both the centre and this group.

  - Strengths and opportunities

The research conducted by this team, whose leader appeared to the committee very dynamic and highly involved in the management of the various research themes, presents a good equilibrium between basic and translational research. There is a clear will to translate rapidly the results of the fundamental studies to clinical applications as shown by initiation of the Therapredict and the OBPM start-ups.

– Weaknesses and threats

The activity of the team is in a very competitive field and as many aspects are dealt with there is a risk of dispersion which might be detrimental to the quality of the basic research conducted. The team would likely benefit from a precise definition of its priorities in terms of fundamental studies and of translational research.

The team is localized in Angers, away from most other teams of the Center, which limits its participation to the life of the Center.

– Recommendations

As many researchers of the team have a high teaching duty they might think to ways to devote more times to research (IUF application for instance..). Also the team should try to hire foreign post-docs. Finally it is important for the group to maintain and develop close links and collaborations with the other CRCNA teams.

Team 13 : Nuclear oncology

Team leader : Mr Jacques BARBET

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 2.4 and 2.7 of the application file)	5	7
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	6	
N6: Number of Ph.D. students (Form 2.8 of the application file)	6	
N7: Number of staff members with a HDR or a similar grade	7	8

- Appreciation on the results

This team has pioneered the use of monoclonal antibodies for radio-immunotherapy (RIT) and metabolic dosimetry in a number of areas. Original findings from this team have demonstrated that RIT is potentially efficient also in solid tumours; from scientific points of view some results are original and promising

Synergistic association of targeted therapy and RIT

CD 138 targeting and its improvement

Bispecific targeting

animal (DIGIMOUSE) and patients (Oedipe) Dosimetry (this is a unique expertise).

Despite a quiet and risky research activity, this team has an impressive publications track record. Among more than 80 publications, about 45 are signed as first and/or last author by a team member. They also wrote a number of reviews. Interestingly, publications do not only concern Nuclear Medicine literature (where they publish regularly in the best journals: for instance 4 papers in J Nucl Med), leading to reach higher impact factors (several first and senior-authored publications in J Clin Oncology, collaborative work in Blood, Cancer Res etc.) and also to increase its international credibility.

A lot of a high quality and stable partnerships are mentioned here, some of them are very relevant (strategic) such as IETU (Institut européen des transuraniens) (cf alpha), Veterinary school (ONIRIS : veterinary animal cancer models , animal imaging), Immunomedics in the US and other centers in Europe.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has a high international visibility as reflected by its participation in European programs such as the TAARC program, COST program etc

It has a strong capability to raise funds [ARRONAX cyclotron, IncA DHOS PHRC (there is a very significant clinical research programs granted by the DHOS)]

Two spin-out companies have been created

They have recently recruited two new scientists (1 MCU-PH and 1 PU-PH)

- Appreciation on the scientific strategy and the project

The global project is relevant and feasible because it is based on already strong ongoing collaborations with clinicians and various research teams, in the same unit or elsewhere. There are still ongoing granted applications and a strong local support (Region Canceropole, Université, CLCC and CHU).

The Project is very clear; there is a high capability to transfer this activity into clinic.

This team will benefit from the Arronax cyclotron deemed to provide novel radionuclide conjugates for targeted therapy, which is a unique strength of this team. In addition, the cyclotron should also generate more relevant biomarkers for new areas of oncological imaging such as hypoxia. The usefulness of a close collaboration with Oniris for small animal imaging has been also well recognized

The alpha therapy project is very original, because of the associated research programs about immune response and microdosimetry it is even more interesting and promising, providing a very competitive project.

ImmunoPET based program is also original and well integrated into the global strategy.

- Conclusion :

  - Summary

This team has pioneered the use of bispecific mocolonal antibodies for RIT

It is the most experienced team in France and one of the most famous in the world in this field

Basically this team has a translational research activity in Beta RIT and since recently, in alpha therapy. This team is also developing some interesting novel PET imaging (phenotype imaging and immunoPET)

  - Strengths and opportunities

Multidisciplinary Expertise (chemistry radiochemistry dosimetry); In-house strong relationship (radiobiology immunology).

High level of foreign Academic collaborations, close relationships with small or big pharmaceutical companies

Obviously Arronax cyclotron – the only one of its kind in the world, provides a tremendous opportunity. This team has also the capability to coordinate valorisation process gathering the INSERM, the University Hopsital and the Comprehensive cancer center.

The collaboration with ONIRIS is very important because of the use of animal model and then animal imaging, but also because veterinary animal models could help better understand the role of the host in RIT efficacy and toxicity compared to xenografted models).

This team is attractive (cf 1 MCU PH and 1 PUPH recently recruited)

– Weaknesses and threats

The development of new tracers/drugs forms an essential part of the research projects. Such developments are usually time-consuming, expensive and sometimes could be hampered by the increasingly strict governmental regulations.

Even though the development of PET imaging is important in nuclear oncology and this team has developed very well in this field, it would be wise to allocate resources carefully so as not to hamper the international leading position of this team in the field of RIT.

– Recommendations

Keep focused on MoAB based vectorisation, MoAB alone or grafted on nanovectors

PET activity should be better focused on immunoPET (direct link with RIT) or on original imaging biomarker as surrogate of efficacy or prognosis factor for RIT.

As for other targeted therapies, RIT needs dedicated biomarkers of efficacy, improved patient screening process (not only based on target expression) and validation of synergistic association. This team is one of the few able to provide an appropriate rationale about radiobiology and immune response pathways involved in RIT, this is mandatory for high impact publication and development of RIT.

Collaboration with team 14 should be maintained because endothelial cells response to irradiation could also have an implication in endocrine tumors' response to RIT.

It is advised that the day-to-day running cost of a dedicated research cyclotron like the Arronax would be substantial and thus early consideration of income generating activities such as producing radionuclides with commercial potential would help ensure a healthy development of this team.

In Summary, Team 13 is well-established, has earned its internationally renowned reputation in high quality Nuclear Oncology research through original research productivities as reflected by the amount of academic activities and high impact publications. It is fair to rate this team within the top 10% in the field internationally.

Team 14: Endothelium radiobiology and targeting

Team leader: Mr François PARIS

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 2.4 and 2.7 of the application file)	3	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.8 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

This team tries to improve the knowledge about the efficacy and toxicity of medical irradiation. From a medical point of view these are very relevant issues. More interestingly, this team is developing original research about non tumoral tissue (endothelial cells). This team has made several significant contributions in the field of radiobiology and radiotherapy, with a strong emphasis on the response of the endothelium and on the involvement of sphingolipid metabolism. This is of particular importance because it may lead to improve the protection of the healthy tissues. Approaches concerning endothelial cells and the modulation of endothelial cell radiation -induced apoptosis seem to be original and very promising.

This is a young team created in 2008, but with already about 15 original publications in peer- reviewed journals. Seven of them involve a team member as first and/or senior author in good journals such as Cancer Res, Mutation Research, Clin Cancer Res, Am J Physiol. Collaborative studies have been published in Blood, J Nucl Med, J Pathol etc. Team members have been invited to give 15 conferences

Since its creation this team has conserved previously established partnerships and is willing to develop collaborations with medical physics, and clinicians (radiation therapist).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Keeping in mind that this is a young team, attractiveness appears quite good. Indeed:

The collaboration with IRSN is very relevant; as its expertise in radiation toxicity is one of the most famous in the world, offering a significant probability of international collaborations

The team was able to attract 2 new members in 2010 (one is the head of the medical physics unit). This is very important because it will contribute to secured dosimetry capability and translational activity in radiotherapy

They were able to get a significant competitive funding through InCa PAIR Prostate.

Radiobiology and radiation toxicity are under-investigated areas. Indeed, there are a relatively small number of research teams working in these fields. The team leader has acquired extensive training/working experience at internationally leading centres including Oxford University, MSKCC. The committee understands that there have been stable and promising collaborations with these centres.

A start-up has been created in 2009 (Atlab)

- Appreciation on the scientific strategy and the project

The global project is relevant and feasible because it is based on very clear and logical scientific objectives; there is a high capability to transfer this activity into clinic.

This team is keen to benefit from the Arronax cyclotron deemed to provide more relevant biomarkers for hypoxia. It has also well recognized the usefulness of a close collaboration with the Veterinary School (Oniris) for small animal imaging

- Conclusion :

– Summary

This a young team with an already strong scientific track record with robust and original results. This team has already proven its skill for transfer in clinic

– Strengths and opportunities

The more interesting scientific activity concerns the study of the various pathways induced from endothelial cells irradiation. The collaboration with IRSN in the field of radiation toxicity is a good opportunity for further international collaboration and may also improve the team visibility in this domain. The new building will certainly optimize the collaborations.

– Weaknesses and threats

There are 4 scientific objectives, each of them having on average two main topics. Even though there are many synergistic activities, this seems too much for a team with only 9 team groups members and only two technicians.

– Recommendations

To develop close collaboration with team 13 because this team used slow proliferating tumours model, exposed to low dose rate irradiation, these experimental conditions may help to elucidate the mechanisms of endothelial cells response to irradiation. In addition, imaging expertise from Team 13 could potentially substantially enhance the quality of imaging related research projects, such as hypoxia imaging.

Keep focused on anti-O-Ac-GD2 antibody and anti-Gb3 antibody

The clinical research programs are time consuming, thus they should be determined accordingly to the scientific needs.

Team 16 : Biomarkers of metaplasia and dysplasia of epithelia

Team leader: Mr Jean-François MOSNIER

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	5	7

- Appreciation on the results

This is a multidisciplicary team focusing on the identification of the elements that subordinate phenotypic and functional cellular epithelial alterations during “non canonical intestinal oncogenesis” and during loss of immune homeostasis.

The team has made significant contributions :

-The main results obtained in the last 4 years were based on the use of a a large panel of colon cancer cell lines (used for in vitro studies), a large tissue collection of colon cancer and inflammatory bowel disease (IBD) with clinical and genetic annotations and in particular the availability of a unique ex vivo explant culture model. This translational research resulted in : the demonstration of the coexpression of ADAM17 and EGFR in most human colonic carcinomas, accounting for an autocrine-paracrine loop of survival-proliferation of tumor cells. This team has also shown that ADAM15 down-regulation was associated with EMT and with poor prognosis as well as the involvement ADAM15 in the tissue remodeling associated with inflammatory bowel diseases. Using an explant culture approach, the team has demonstrated that IL10 and TGFb are essential in maintaining the local immune homeostasis. A first demonstration of the existence a tolerogenic immunomodulatory loop maintained by resident cells of human intestinal mucosa was provided.

-The team has produced more than 40 publications around the thema topics, half of them involving a team member as first and/or senior author. Most of them were published in median to good impact specialty journals such as Lab invest, FASEB J, J Pathol, Br J Pharmacol. A major paper was published in the J. Clin Invest.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

- The recruitment of phD students and post docs is significantly weak.

- Fund raising has been limited.

- The team participates very little to networks and has no active foreign collaborations

- Appreciation on the management and life of the research unit:

At this stage of organization, it is not exactly clear whether the team leader is effectively coordinating all the programs.

Professors and assistant professors have regular teaching activities in faculty of medecine, at both the undergraduate and graduate levels. Their contribution to the proposed project is not clear.

- Appreciation on the scientific strategy and the project

2 main themes will be addressed by combining different experimental approaches with a significant clinical interface:

a-the non canonical pathways of colorectal oncogenesis: the specific aim is to characterize and clusterize using immunohistochemistry on tissue-microarrays the biomarkers expressed by lesions on interest and to explore in particular the role of the Notch pathway in the oncogenic process. This group is very medically oriented.

b-the role of innate immunity in the onset of a Th1 response elicited by resident cells of the human intestinal mucosa upon breakdown of the tolerogenic state exerted by IL10 and TGFbeta: several questions are addressed:

-the mechanism leading to the conversion of resident intestinal mucosa cells into pro-inflammatory cells eliciting a Th1 (IFN□) response upon breakdown of IL10 and TGFB tolerogenicity.

-Delineate how the combined activation of innate and adaptive immune system trigger a Th1 response and in particular to identify the bacterial pattern recognition receptos (PRR) including TLR and NOD like receptors involved in the initiation of Th1 response.

-The description of the proposed research needs further clarification. Although of potential interest, the description of the project is too short, very vague in some parts (what type of experiments will be done). The connection between the two subgroups of the team should be increased. Putting together different research teams (pathologists, basic scientists and geneticists) working should result in a strong potential. Nevertheless, the role played by the participants in the implementation of the scientific program is quite unclear in particular the geneticists.

- Conclusion :

  - Summary

This is a multidisciplinary team with a strong expertise in developing and exploiting in vitro models and the retrospective and prospective exploitation of tissue collections. The team has set up a translational research continuum between human tumor bank and basic research and has made significant contributions during the last 4 years.

However the team is lacking scientific visibility and is not well integrated in the CRCNA. The project is not in the present form completely convincing. The team should improve the coherence of its project and has to overcome some challenges in particular an increase in the critical mass, interaction with other teams at the CRCNA and finally to improve the scientific lead.

The structure of the team does not seem to be viable as an independent team to achieve the project. There are some doubts about the competitiveness of the group without the addition of strong scientific expertise.

- Strengths and opportunities

-They have been able to put together research teams working on colon cancer and inflammatory bowel diseases with a strong expertise in developing and exploiting in vitro models and the retrospective and prospective exploitation of tissue collections;

-The team has set up a translational research continuum between human tumor bank and basic research.

- Weaknesses and threats, and recommandations:

Several issues have to be addressed:

-The scientific lead has to be revisited

- The critical mass should be increased: there are only few staff scientists and few PhD and post docs. The integration of two CR1 INSERM researchers does not appear to provide a real added value to this team.

-Subgroup leaders need to be identified and contribution of the participants to the project should be clarified.

-The internal interaction with the center and in particular with team 12 should be strengthened.

-Team integration within CRCNA appeared weak.

-The team should further interact with other teams of the center, expand and to promote junior scientists.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
CENTRE DE RECHERCHE EN CANCEROLOGIE NANTES-ANGERS	**A**	**A**	**A+**	**A**	**A**
MOLECULAR BASES FOR TARGETED THERAPIES IN MULTIPLE MYELOMA AND MANTLE CELL LYMPHOMA [LE PENDU-AMIOT]	A	A	Non noté	A	A
NUCLEAR ONCOLOGY [LE PENDU-BARBET]	A	A+	Non noté	A+	A+
: IMMUNOBIOLOGY OF NON-CONVENTIONAL T LYMPHOCYTES [LE PENDU-BONNEVILE]	A	A+	Non noté	A+	A+
TARGETED THERAPIES IN COLORECTAL CANCER [LE PENDU-COQUERET]	A	A	Non noté	A	A
INNATE IMMUNITY, IMMUNOPATHOLOGY AND IMMUNOTHERAPY [LE PENDU-DELNESTE]	A	A	Non noté	A+	A+
CLINICAL AND TRANSLATIONAL RESEARCH IN SKIN CANCER [LE PENDU-DRENO]	B	A	Non noté	A	A
BIOLOGY OF DENDRITIC CELLS AND IMMUNOTHERAPEUTIC USE IN ONCOLOGY [LE PENDU-GREGOIRE]	B	A	Non noté	B	B
CYTOKINES AND RECEPTORS IN IMMUNO-HEMATO-ONCOLOGY [LE PENDU-JACQUES-HERMOUET]	A	A	Non noté	A	A
CELL SURVIVAL AND TUMOR ESCAPE IN BREAST CANCER [LE PENDU-JUIN]	A	A	Non noté	A+	A
ANTI-TUMOR T CELL RESPONSES AND IMMUNOTHERAPY [LE PENDU-LABARIERRE]	A+	A	Non noté	A+	A+
GLYCOCONJUGATES IN IMMUNE RESPONSES [LE PENDU-LE PENDU]	A	A	Non noté	A	A
INTEGRATIVE ONCOGENOMICS OF MULTIPLE MYELOMA PATHOGENESIS AND PROGRESSION [LE PENDU-MINVIELLE]	A	A	Non noté	A	A
GRAFT-VS.-HOST REACTIONS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION [LE PENDU-MOHTY]	A	A+	Non noté	A	A
BIOMARKERS OF METAPLASIA AND DISPLASIA OF EPITHELIA [LE PENDU-MOSNIER]	B	B	Non noté	B	B
ENDOTHELIUM RADIOBIOLOGY AND TARGETING [LE PENDU-PARIS]	Non noté	A	Non noté	A	A
APOPTOSIS AND TUMORAL PROGRESSION [LE PENDU-VALLETTE]	A	A	Non noté	A+	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE NANTES

PRÉSIDENCE DE L'UNIVERSITÉ
DIVISION DE LA RECHERCHE
ET DES ÉTUDES DOCTORALES

Nantes, mardi 12 avril 2011

REF : JG/PTi - 2011 RECH N°436
SUIVI PAR : Jacques GIRARDEAU
Objet : Rapport d'évaluation - S2UR120001446 - CENTRE DE RECHERCHE EN CANCEROLOGIE NANTES-ANGERS - 0440984F

LE PRÉSIDENT

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
AERES

Monsieur le directeur,

Je vous prie de trouver ci-joint les observations de portée générale de Monsieur Jacques LE PENDU concernant le rapport d'évaluation de son unité « Centre de recherche en cancérologie Nantes-Angers », UMR 892, observations que j'approuve bien évidemment.

Je vous prie d'agréer, Monsieur le directeur, l'expression de mes sentiments les plus cordiaux.

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Nantes, April 11th 2011

To the attention of AERES

We thank the members of the AERES evaluation committee for their thorough review of the CRNCA and for the quality and rigor of their work. We are pleased to note that the global appreciation is very positive and that the committee considers that the center has a strong potential to become a center of excellence in cancer research in France. The committee made some recommendations that will be taken into account and will be the focus of future efforts.

Although we are in general agreement with the issues raised by the committee, we would like to clarify or stress a few points. The committee notes that "Despite of a very good scientific output testified by a large number of publications, the center still lacks publications of very high visibility in prestigious journals". We agree with this statement, yet we would like to stress the very high involvement of all CRCNA teams in transfer activities either clinical or industrial, an aspect which in our view has been somewhat underestimated by the committee. Indeed, CRCNA teams were involved in a total of 56 clinical trials, including 35 (and not 17 as stated in the report) phase I/II trials, 15 biological trials and 7 phase III trials directly derived from the teams basic work. This high involvement in translational research is testified by the success of CRCNA teams in raising specific highly competitive grants for clinical trials (16 PHRC, 9 DGOS-INCA, 2 EU and 1 ANRS) and by many publications in highly visible clinical journals (in particular 20 publications in Blood and 15 in Journal of Clinical Oncology). In addition to their involvement in patents and licenses, CRCNA teams created 5 start-up companies instead of 2 as stated in the report : Therapredict (team 12), ODMP (team 12), Atlab Pharma (teams 13 & 14), Cytune Pharma (team 6), Myelomax (team 10). Moreover, the transfer of know-how from team #6 to Ipsogen, led to the development and marketing of the JAK2V617F MutaQuant kit (the sole quantitative kit for JAK2V617F on the international market). This last point was missing in our report.

Moreover CRCNA teams are leading the development of cell therapy at the Regional level since the dedicated core facilities of the *CIC Biothérapie* called DTC (*Développement et Transfert Clinique*) and UTCG (*Unité de Thérapie Cellulaire*) have been set up and are coordinated by teams 4 and 2 respectively. Together these core facilites allow the preclinical developments and production of cells at clinical grade for cell therapy clinical trials.

Concerning our failure to hire promising junior-scientist and young groups from outside, and the absence of a policy on the matter, we would like to mention that this is clearly due to a lack of space. We are fully aware of this limitation and actively working with the University of Nantes, the University Hospital, the Cancer Clinical Center and the local authorities in order to obtain new facilities in the next few years.

TEAMS SPECIFIC COMMENTS :

Team 2 : We acknowledge the comments and recommendations of the committee. We just would like to reassure the committee on the continuation of the strong collaboration we have with team n°3 since 1992. Together we will continue the ongoing program on adoptive immunotherapy and the development of new clinical trials in melanoma.

Team 3 : First, we would like to thank the evaluation team for their time and excellent expertise of our work. The aims of this letter are to clarify some organizational points and to comment on some of the recommendations that were made.

1."International visibility may be further improved" : We are aware that this specific point needs to be improved. We are currently developing international collaborations in the field of vaccination and adoptive cell transfer therapy, that should enlarge our international networks. Recent publications have been made in collaboration with foreign co-workers :

- Olofsson PS, Soderstrom LA, Wagsater D, Sheikine Y, Ocaya P, Lang F, Chen L, Rudling M, Aukrust P, Hedin U, Paulsson-Berne G, Sirsjo A, Hansson GK. CD137 is expressed in human atherosclerosis and promotes development of plaque inflammation in hypercholesterolemic mice. *Circulation* **2008** 117 : 1292-1301. **(Sweden)**
- Godet Y, Bonnin A, Guilloux Y, Vignard V, Schadendorf D, Dreno B, Jotereau F, Labarriere N. A new tyrosinase epitope recognized in the HLA-B*4002 context by CTL from melanoma patients. *Cancer Immunol Immunother.* **2009**; 58:271-80 **(Germany)**
- Godet Y, Desfrançois J, Vignard V, Schadendorf D, Khammari A, Dreno B, Jotereau F, Labarrière N. Frequent occurrence of high affinity T cells against MELOE-1 makes this antigen an attractive target for melanoma immunotherapy. *Eur J Immunol.* **2010** 40:1786-1794. **(Germany)**
- Godefroy E, Manches O, Dreno B, Hochman T, Rolnitzky L, Labarrière N, Guilloux Y, Goldberg J, Jotereau F, Bhardwaj N. Matrix Metalloproteinase-2 Conditions Human Dendritic Cells to Prime Inflammatory T(H)2 Cells via an IL-12- and OX40L-Dependent Pathway. Cancer cell **2011**;19(3):333-46. **(USA)**

Furthermore, N. Labarriere and F. Lang have been recently invited with B. Dreno to publish a review in "Immunotherapy": Labarriere N, Khammari A, Lang F, Dreno B. Is antigen specificity the key to efficient adoptive T cell therapy? Immunotherapy, in press, **2011**.
The new team leader will put specific efforts to improve this point by participating in international congresses and initiating new collaborations.

2. "The funding of the situation is not completely clear, in particular with respect to the (expensive) clinical translation of the peptide vaccines and cell therapy products". : The project concerning the production of GMP tools to sort antigen specific T cells is currently supported by a grant from ANR (BiotecS, 2010). The completion of this project will lead to the production of two GMP-batches of HLA/MELOE-1 and HLA/Melan-A multimers, that will be used in a clinical trial, including 20 metastatic melanoma patients. We will apply for a specific grant with B. Dreno from Team 2 to perform this clinical trial in 2012, on the "Hospital program of clinical research". The costs of GMP-batches will not be supported by this grant, as they will be already available.
Concerning the peptide vaccines program, we just submitted an application to an ANR grant (Emergence) at the request of the valorization department of Inserm. Indeed, the strategy of valorization is based on a strong IP position. The successful results from this program will reinforce the transfer potential on the emerging and very active market of anti-tumor vaccine. Some companies are already interested in our expertise on the novel tumor antigen, MELOE-1, but the project needs more *in vivo* data to convince the numerous contacts to acquire options and exclusive licenses of exploitation for the completion of vaccination trials supported by these companies.
3."Strong link with team 2 must be maintained to ensure continued high profile productivity in the translational field" : It appears obvious for our two teams that the success of our translational research

programs depends on a tight collaboration with team 2. As underlined by the committee, this synergy translated in very competitive results in this field. It is thus in the interest of both teams to keep on working that way. The rational for splitting into two independent teams was the setting-up in the center of a group of clinical research on melanoma, based on a wider program involving other teams of the U892.

Team 4 : Since the site visit, two new articles have been accepted for publication in *European Respiratory Journal*, and one in *American Journal of Pathology*. One manuscript is under minor revision in *Current Cancer Drug Targets*, and one is (re)submitted in its final revised form to *Vaccine*.
In addition, we recently registered a collection of 20 mesothelial cells and 4 mesothelioma cells in rats (at Migratech database (https://migratech.inserm-transfert.fr), MT0481 to MT0495 and MT0503 to MT0511).
A T cell clone was established last year, which is specific to MUC-I (patent licensed by Inserm Transfert to Transgène : n° 10744A10). We also validated a *Screening and characterization of new histone deacetylase inhibitors* (HDACi) using **BRET** based assay : MT0497.
In term of clinical transfer, we would like to highlight the very strong implication of the team leader in the set up and operation of a new core facility dedicated to the development of clinical protocols for cell therapy (DTC), which works in close collaboration with the Cellular Therapy Unit based in Nantes hospital (UTCG unit) in providing technological support within a context of traceability and quality insurance according to ISO 9001:2000 norm.

Team 6: We thank the committee for an overall very positive report on our team. Team 6 is indeed very active both in "immunology" projects and in "cancer" projects. This response simply aims to correct a couple of factual errors and to better describe the strengths of Team 6 (we feel that the cancer projects were somewhat under-reported).
The team recruited two (not one) new tenured researchers, to extend the expertise of the team and to develop new projects. One develops and extends IL-15 projects; the other develops a new, transversal, proof-of-concept project (Specificity of monoclonal immunoglobulin characteristic of MGUS and myeloma).
Both team leaders are internationally recognized experts in their respective fields, IL-15 and myeloproliferative neoplasms (MPN). One initiated, and coordinates, a new European network on the molecular diagnosis of MPN (COST action BM0902 = MPN&MPNr-EuroNet).
"Weakness: *The project dealing with JAK2 mutations might be over-ambitious based on the actual expertise of the group and the competition in the field".* In fact the group was the first to identify multiple JAK2 mutations, and to show that some JAK2 mutants lead to distinct signaling and different disease phenotypes (Leukemia 2010). One reason is that we developed highly sensitive assays, and that these techniques are necessary to detect JAK2 mutants other than V617F (several were identified, currently being explored). Thus the group is a leader in this field of research, ahead of the competition in this respect. One proof is that leading research labs in the MPN field (AR Green in Cambridge; AM Vannucchi in Florence; S Schnittger in Münich) registered collaborators to a training school dedicated to the detection of JAK2 mutations initiated by the PI responsible for the "JAK2 mutant" project. This training school, organized within MPN&MPNr-EuroNet, is scheduled for May 11-13, 2011 (see www.mpneuronet.eu). Moreover, the group recently generated new results on JAK2 mutation and rearrangement, of sufficient importance to be the basis of a manuscript, currently in the last stages of revision, which we plan to submit to a high profile journal.

Team 7 : We thank the reviewers for their thorough evaluation of our project.
We wish to clarify how we envision incorporating animal models to test the therapeutic potential of Bcl-2 inhibitors. We have initiated a collaboration with the Preclinical Investigation Laboratory at Insitut Curie (Paris, Dr D. Decaudin) to perform, on site, *in vivo* studies of transplantable human breast

cancer xenografts developed in this laboratory (Marangoni et al., Clin. Cancer Res., 2007, 13, 3989-98). We, in particular, intend to investigate, through this collaboration, the role Bcl-2 family members play in the response of luminal mammary tumors to therapy (application to INCa call, *INCa Translationnel 2011,* coord. Dr Decaudin).
Additionally, we have initiated collaboration with the Nantes Clinical Cancer Center and with the Nantes Veterinary School. This collaboration will allow us to study *spontaneous* mammary tumors from cats and dogs. We intend to perform functional tests, (including *ex vivo* ones similar to these developed using human patient samples as described in our report) after a first, ongoing, phase of phenotypic and molecular classification of these tumors. This first necessary phase of compared pathology obtained funding by INCa (Recherche Translationnelle INCa-DGOS 2010, coordin. Dr M. Campone).

Team 9 : We thank the experts for their thorough analyses. We do not have specific comments on the report. As noted by the experts, the number of PhD students and post Doc is quite low but this is coincidental as it was substantially higher last year and, hopefully, it should increase by the end of 2011.

Team 10 : We acknowledge the committee for its comments. However, we are surprised by the statements « no translational tasks are proposed » and « Basic /translational research is lacking » since the team focused on biological and clinical assessment of novel therapies: (i) proteasome inhibitor and immunomodulator agent (ImiD) in multiple myeloma and mantle cell lymphoma as evidenced by the following clinical trials :

Phase II Phase 2, multicenter, randomized open-label study to determine the efficacy of lenalidomide (REVLIMID®) versus investigator's choice in patients with relapse or refractory mantle cell lymphoma. Promotor: Celgene. Co-investigator: Le Gouill. Inclusion: 140 patients Start: 4/2009. Funding: Celgene.

Phase I A multicenter Phase IB dose escalation study to evaluate the safety, feasibility and efficacy of the Temsirolimus (Torisel™)-CHOP-Rituximab (T-R-CHOP), Temsirolimus-FC-Rituximab (T-R-FC) and Temsirolimus-DHA-Rituximab (T-R-DHA) for the treatment of patients in relapsed/refractory Mantle Cell Lymphoma Promotor: GELA. Principal Investigator : Le Gouill S. Start: 2011. Funding: Pfizer.

Phase I/II. "Phase I/II trial of Carfilzomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma. » Principal Coordinator : P. Moreau and Co-investigator: S Le Gouill. Promotor: CHU de Nantes. Start: 10/2010 Inclusion: 12 patients. Funding: Onyx.

In addition, team 10, has reinforced its ability to conduct translational projects. Indeed, our recent identification of a shared therapeutic target in Myeloma (Bodet et al Blood in revision) and Mantle cell lymphoma (Touzeau et al. submitted) according to molecular heterogenity (Moreaux et al, Heamatologica 2011) is the rationale of a phase I/II clinical trial that is in advanced discussion with Roche/Genentech. This trial, which includes biological monitoring, will be conducted in the Clinical Research Unit headed by Pr S Le Gouill (URC, labelised by the INCa-CLIP2 program 2010) in the Hematology department of Nantes Medical University. A translational grant application in Mantle cell lymphoma (preselected) is pending at Inca. In addition, a Post-Doc fellow has joined our group since 01/2011.

- Moreaux J and al, A high-risk signature for patients with multiple myeloma established from the molecular classification of human myeloma cell lines. Haematologica. 2011; 96:574-82 ;
- Bodet L, and al ABT-737 is highly effective against molecular subgroups of multiple myeloma.

Blood in revision ;
- Touzeau C, and al. ABT-737 induces apoptosis in mantle cell lymphoma cells with a Bcl-2^{high}/Mcl-1^{low} profile and synergizes with other anti-neoplastic agents. Submitted.

Teams 10 and 11 : Concerning the specific recommendation to "clarify thematic positioning and interactions " between teams 10 and 11, we would like to stress that teams 10 and 11 address two complementary aspects of myeloma translational research. Yet, we cooperate within the CERM (Centre d'Etude et de Recherche sur le Myélome) and apply together for a grant application under the call of Inca "Centres de Références cancer rare"

Team 12 : We would like to thank the members of the committee for their advices concerning our future projects. Focusing research priorities as well as applying to IUF or CNRS/INSERM delegations are effectively important goals that our team will follow, as stated by the committee.

Team 15 : We are grateful to the AERES committee for their positive evaluation of the Team. We concur with the recommendation that recruiting full-time young scientists is a priority.

Team 16 : I read with great interest the remarks and criticisms raised by the AERES committee. With all due respect, I was most dismayed to read a number of statements that we feel quite unfair and misleading, for the reasons detailed below.

- Appreciation on the impact….

- "*The recruitement of phD students and post docs is significantly weak*": true. However the "EA" label turns out not to be so attractive to hire post docs and PhD students and it is one of the reasons why we consider the opportunity to join the CRCNA.
- "*The team participates very little to networks and has no active foreign collaborations*". On reading slide 6 of my presentation (collaborations), it is clear that we have several international collaborations and that we participate in international programs. In addition, from our list of publications, these collaborations are productive. Examples (number of publications since 2005:
- D. Merlin (EMORY university Atlanta USA): (with Mosnier and Laboisse) 5 publications
- U. Hopfer (Case Western University, Cleveland, Ohio) (with Laboisse): 3 publications
- L Augenlicht (Albert Einstein cancer Center, NY) (with Laboisse):: 1 publication
- International Networks: Participation of Bezieau S and Küry S to a genome-wide association scan based on an internationally recruited cohort of patients (publications: Theodoratou et al. **Br. J. Cancer** 103, 1875, 2010; Zanke et al. **Nature Genetics**, 39, 989, 2007)

Moreover our team has been involved in the exploitation of a tissue bank within a french network that led to the identification of a novel susceptibility pathway to Crohn's disease (publication in Nature Genetics: Brest P et al, **Nature Genetics**, 43, 242, 2011- Comment in the same issue of Nature Genetics).

- Appreciation on the management and life….

- "*At this stage of organization, it is not exactly clear whether the team leader is effectively coordinating all the programs*": As the leader of the team my objective is not to coordinate (or to interfere with) all the research activities, and I clearly stated this point during my presentation. My objective, as leader of the EA, was 1) to merge the former geneticists' group (former EA3823) with our team on the basis of a research project that I actually lead (and we all did the job: see publications) and 2) to invite a gastroenterologist and a medical oncologist to join us and participate in the CRCNA project. In fact my strategy through these recruitments was and still is to gather a multidisciplinary expertise needed to achieve our projects.
- "*Professors and assistant professors…. Their contribution to the proposed project is not clear*": I assume that the committee infers that some members of the team are not involved in the job. This needs some explanation: in fact our translational research implies different levels of expertise, different levels of involvement depending on the evolution of the project: it is therefore very difficult to define with great precision the task for everybody.

- Appreciation on the scientific strategy

-"*The description of the proposed research is… too short, very vague… Nevertheless, the role played by the participants in the implementation of the scientific program is quite unclear in particular the geneticists*": I would like to put this comment in perspective with the sentence that follows on the same page (under the heading Conclusion: summary) "*This is a multidisciplinary team with a strong expertise in developing and exploiting in vitro models and retrospective and prospective exploitation of tissue collections. The team…has made significant contributions during the last 4 years*". On the one hand our group is quite unable to develop a good research project, on the other hand we were very good during the last few years.

- "*However the team is…not well integrated in the CRCNA*". During my presentation, I provided direct evidence showing strong ongoing collaborative work with teams of the CRNCA. Cases in point:

- Team 3 (F. Jotereau): A member of EA biometadys (C. Bossard) stayed for one year as a post-doc (2009) in Jotereau's team: an article is already published (Sarrabayrouse G et al. **Int. J. Cancer** 2010) and a new one is under submission. This successful collaborative research goes on farther with the submission to the "Canceropôle Grand Ouest" of a collaborative project in the continuity of the post-doc program . On the other hand Team 3 of the CRCNA and EA Biometadys shared recently two successive grants from DHOS for a collaborative research project on GI tract cancer.

- Team 4: We already have an emerging collaboration with this team based on the deciphering of the cytokine network in the GVH: both teams have very complementary skills and preliminary results of this collaboration are very exciting.

Naturally we expect from our integration within the CRCNA to further enhance and extend these ongoing collaborations and this is the main reason why the merging of our team with the Center has been strongly encouraged by the Nantes University and the current and future director of the CRCNA.

- Weaknesses and threats and recommendations

- "*the scientific lead has to be revisited*". All I can say is that the team trusts me.
- "*The integration of two CR1 INSERM researchers does not appear to provide a real added value to this team*". Added value of A. Jarry since 2006 in terms of publications : 13 publications and among them, first author in *J. Clin Invest.* As for Frederique Souaze, she joined later our team and her scientific production is somewhat delayed.
- *"Subgroup leaders need to be recruited…, the internal interaction with the center…. team integration with the CRCNA appeared weak… the team should further interact with other teams"*: all these issues have already been addressed as specific points in this document.

In conclusion, our decision to join the CRCNA is guided by several strategic and scientific reasons : our team opens a window to the tumorothèque, we provide an expertise in the domain of clinico-pathological and genetic annotations of cohorts of patients with cancer, we provide also an expertise in the pathological annotation of animal models, the main focus of our research is on cancer, we have an ongoing fruitful collaboration with a team of CRCNA and have already started another collaboration with another team of CRCNA.

Team 17 : We would like to thank the assessors for their overall positive feedback related to this team, highlighting the *"expertise"*, the *"strong international visibility"*, the *"capacity of the team leader to raise numerous and important funding during the past few years"*, and the *"impressive number of publications with more than 60 papers in the last 5 years"* including *"11 papers in very good journals"*.
Also, we have much appreciated that the committee acknowledged the *"strong potential"* of the *"highly dynamic and enthusiastic"* team leader, *"due to a very good fundamental-clinical interface and design of challenging projects"*.
Nevertheless, we would like to further address the following issues that were raised during the assessment process:

1- *"The team leader has been leading a research project in previous team #4 during the past two years with 1 PhD student and 1 technician on histone deacetylase inhibitors on DC phenotype and function in vitro. Although some results have been obtained they still appear quite preliminary*": From that perspective, we would like to mention that since the assessment by this committee in January 2011, two manuscripts related to the impact of HDACi and hypomethylating agents on DC function both in vitro and in patients with haematological malignancies, have been prepared for publication purposes. Also, some of the data related to the status of Th subsets and pDCs in gut GVHD are currently submitted to the journal BLOOD for publication purposes. These manuscripts are available to the committee upon request.

2- *"This is a new team with 3 technicians and 3 PhD students. The size of the team is therefore relatively small and it is too early to evaluate the management of the team. It is also too early to evaluate the capacity of the team leader to supervised PhD students (3 ongoing PhD, past-PhD supervision not mentioned).*":

Despite his relatively young age (40 years), the team leader has a well established track record in terms of student management and supervision. He already obtained his "Habilitation à Diriger les Recherches (HDR)" in 2005 and was the supervisor/director for the following students, all of whom have already successfully obtained their PhD thesis and Masters M2: J. Veran (PhD defended in 2005; Université de la Méditerranée, Marseille), N. Ben Mami (PhD defended in 2007; Université de la Méditerranée, Marseille), AM. Farres (PhD defended in 2007, Université de la Méditerranée, Marseille), J. Frikeche (Master M2 defended in 2008; Université de Nantes), A. Clavert (Master M2 defended in 2009, Université de Nantes) ; E. Brissot (Master M2 defended in 2010, Université de Nantes).

The team leader has also supervised several medical students and fellows in their research projects and medical thesis: H de Lavallade (2006; Université de la Méditerranée, Marseille); N. Blin (2007, Université de Nantes); X. Cahu (2009, Université de Nantes); ML Couec (2009, Université de Nantes); V. Laurent (2010, Université de Nantes);

The team leader has also been the "rapporteur" of several PhD thesis and HDR diplomas, further highlighting his expertise in terms of scientific teams management: C. Jiguet-Jiglaire (PhD 2006 ; Université Paul Sabatier, Toulouse) ; M. Condemine (PhD 2007; Univeristé de Montpellier I); N. Montcuquet (PhD 2008, Université de Franche Comté) ; S. Thiant (PhD 2010, Université de Lille 2); J. Ertault de la Bretonniere (HDR 2008 ; Université de Lille) ; F. Garnache (HDR 2009 ; Université de Franche Comté) ; G. Damaj (HDR 2010, Université d'Amiens) ;

Finally the team leader has obtained a "contrat d'interface INSERM" (50% FTE dedicated to lab research) since 2004 without any interruption, which permitted him to setup a well established daily and routine organization allowing for an efficient and successful management of the students and trainees under his supervision in the lab.

3- *"The team leader has planned to recruit a full-time scientist to firmly establish the group within the next coming years. The team may need some implementation in the future by recruiting a full-time scientist in order to develop the ongoing projects in an effective way.":*

We confirm this point. The future recruitment of a full time scientist is part of the strategic plans of this already very productive team (8 additional papers published since the time of evaluation by this committee in January 2011, of which 2 as first author, and 2 other papers as a senior author including a journal with IF>8).

4- "*The committee suggests to the team leader to try to validate the experimental hypothesis on the role of pDC/Th17 subsets in acute GVHD in animal models allowing mechanistic studies in order to validate the experimental results which will be mainly obtained from human biopsies.*":

We agree with this suggestion, and in this regard, a close collaboration has been established with the group of P. Tiberghien at INSERM UMR645 in Besançon in order to validate our human findings in GVHD murine models. This INSERM unit is among the very few ones in France dedicated to the alloimmune response after solid organ and stem cell transplantation. Based on this collaboration, we are currently testing our human findings in relevant GVHD murine models (ex. Impact of PDC depletion on GVHD severity etc.). Preliminary data are already available.

Team 12 : Targeted therapies in colorectal cancer
Team leader : Pr Olivier COQUERET

Response:

We would like to thank the members of the committee for their advices concerning our future projects. Focusing research priorities as well as applying to IUF or CNRS/INSERM delegations are effectively important goals that our team will follow, as stated by the committee.

Administrative corrections:

. Mistakes in the staff members table page 39:

There is a mistake in the number of engineer and technicians having a tenured position, the N4 and N5 lines are not exact and should be corrected to:

N4: Number of engineer and technicians with a tenured position: 6
N5: Number of engineer and technicians without a tenured position: 1

. Mistakes in the PhD members table:

There is a mistake in the number of PhD, the N6 line is not exact and should be corrected to:

. Number of PhD students (past): 8
. Number of PhD students (Future): 4

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